DEVELOPMENTS IN MICROBIOLOGY

INFECTIOUS DISEASES: SMART STUDY GUIDE FOR MEDICAL STUDENTS, RESIDENTS, AND CLINICAL PROVIDERS

SAIF UL ISLAM

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Infectious Diseases

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Developments in Microbiology

Infectious Diseases

Smart Study Guide for Medical Students, Residents, and Clinical Providers

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Preface

Infectious disease is a difficult subject. Remembering bacteria, viruses, fungi, parasites, and their treatments are difficult tasks; which antibiotic or antiviral to choose or what dose should be given requires years of practice and knowledge.

This book attempts to concise the knowledge and information of infectious diseases into a step-by-step process that would be easy to understand, remember, and use in a clinical setting. High-yield information is presented for students, residents, and practicing providers to help their everyday clinical practice. This book is unique because it combines medical and pharmacological information about infectious diseases into one. It is like one-stop shopping.

The book is written in a nontraditional style for rapid understanding and assimilation. Most of the chapters are presented with tables, figures, and summaries for better comprehension and visualization. Non-clinical and lengthy discussion are avoided to reduce the learning time and pressure, and at the same time provide necessary clinical knowledge and information.

This book is organized for quick and easy-to-retrieve information for all professionals whether they are students, residents, physicians, pharmacists, or nurses.

Images are provided where possible and can also be accessed at www.images.google.com.

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Note: Every effort is made for the accuracy of this book. However, the editor and publisher are not responsible for any error or mistake. It is the sole responsibility of the reader and the practitioner to verify the information presented in this book.

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Common laboratories values

Test	Conventional units	SI units
Arterial blood gases		
PH	7.35–7.45	7.35–7.45
PCO_2	35–45 mmHg	4.7–6.0 KPa
PO_2	80–105 mmHg	10.6–14 kPa
Electrolytes		
Bicarbonate (HCO_3)	22–28 mEq/L	22–28 mmol/L
Calcium (Ca)	8.4–10.2 mg/dL	2.1–2.5 mmol/L
Chloride (Cl)	95–106 mEq/L	95–106 mmol/L
Magnesium	1.3–2.1 mEq/L	0.65–1.05 mmol/L
Phosphate	2.7–4.5 mg/dL	0.87–1.45 mmol/L
Potassium	3.5–5.0 mEq/L	3.5–5.0 mmol/L
Sodium	136–145 mEq/L	136–145 mmol/L
Nonelectrolytes		
Albumin	3.5–5.0 g/dL	30–50 g/L
ALP	35–100 U/L	35–100 U/L
ALT	8–20 U/L	8–20 U/L
Amylase	25–125 U/L	25–125 U/L
AST	8–20 U/L	8–20 U/L
Bilirubin (direct)	0–0.3 mg/dL	0–5 umol/L
Bilirubin (total)	0.1–1.0 mg/dL	2–17 umol/L
BUN	7–18 mg/dL	2.5–7.1 umol/L
Cholesterol	<200 mg/dL	<5.2 mmol/L
Creatinine (female)	10–70 U/L	10–70 U/L
Creatinine (male)	25–90 U/L	25–90 U/L
Creatine kinase—MB	0–12 U/L	0–12 U/L
Ferritin (female)	12–150 ng/mL	12–150 ug/L
Ferritin (male)	15–200 ng/mL	15–200 ug/L
Glucose (fasting)	70–110 mg/dL	3.8–6,1 mmol/L
HbA1c	<6%	<0.06
LDH	100–250 U/L	100–250 U/L
Osmolality	275–300 mOsm/kg	275–300 mOsm/kg

Continued

—cont'd

Test	Conventional units	SI units
Hormones		
ACTH (0800 h)	<60 pg/mL	<13.2 pmol/L
Cortisol (0800 h)	5–23 ug/dL	138–635 nmol/L
Prolactin	<20 ng/mL	<20 ng/mL
Testosterone (male, free)	9–30 ng/dL	0.31–1 pmol/L
Thyroxine (T4)	5–12 ng/dL	64–155 nmol/L
Thyroxine (T3)	115–190 ng/dL	1.8–2.9 nmol/L
TSH	0.5–5 uU/mL	0.5–5.0 uU/L
Hematopoietic values		
ESR (female)	0–20 mm/h	0–20 mm/h
ESR (male)	0–15 mm/h	0–15 mm/h
Hemoglobin (female)	12.3–15.7 g/dL	123–157 g/L
Hemoglobin (male)	13.5–17.5 g/dL	140–174 g/L
Hematocrit (female)	36%–46%	36%–46%
Hematocrit (male)	42%–53%	41%–53%
INR	1.0–1.1	1–1,1
Leukocytes	$4.5–11 \times 10^3$ cells/mm^3	$4,5–11 \times 10^9$ cells/L
MCV	88–100 um^3	88–100 fL
Platelet	$150–400 \times 10^3/mm^3$	$150–400 \times 10^9$ cells/L
PTT	25–35 s	25–35 s
Reticulocytes	0.5%–1.5% of RBC	$20–84 \times 10^9$/L

1 Introduction of infectious diseases

1.1 Bacterial cell

- Prokaryotic cell → no nucleus and no membrane-bound organelle.
- Usually ranges from 0.2 to 2 um in size. However, some species are quite large and can be seen by unaided eye.
- Cell membrane is surrounded by a cell wall made of peptidoglycan. Gram-positive bacteria have a thick peptidoglycan wall, while gram-negative bacteria have a thin wall and are surrounded by an outer membrane that is made of lipoproteins and lipopolysaccharides (LPS) (Fig. 1.1, Table 1.1).
- Lipid-A is a part of the outer membrane of gram-negative bacteria and acts as endotoxin (Fig. 1.2).
- Teichoic acid is found in the cell walls of gram-positive bacteria. It is made of polyglycerol phosphate units that give flexibility to the cell wall.
- Genetic material: No membrane-bound nucleus. Chromosome is usually consisted of circular double-stranded DNA genes for protein synthesis. Some bacteria may have linear DNA or more than one chromosome.
- Other structures such as mitochondria, Golgi complex, and endoplasmic reticulum are unbounded and scattered in the cytoplasm.
- Ribosome comprises 2 subunits, 50s and 30s.
- Plasmid: Circular double-stranded DNA that independently divides and carries gene for special function such as drug resistance. Plasmid passes to daughter cell or to the other bacteria of different species.
- Bacterial cell reproduces asexually by binary fission.
- Some bacteria form endospores that are dormant form of bacteria and are highly resistant to severe conditions such as heat, ultraviolet (UV) radiation, and disinfectants. Example: *Bacillus anthracis*.

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1.2 Difference between gram-positive and gram-negative bacteria

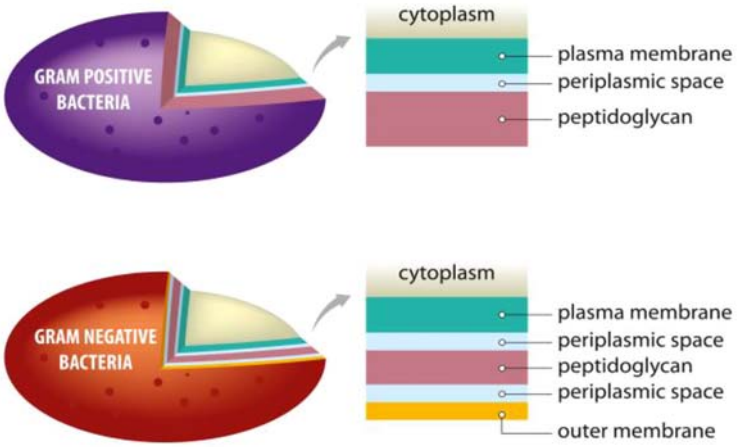

FIGURE 1.1 Difference between gram-positive and gram-negative bacterial cell wall.

Table 1.1 Difference between gram-positive and gram-negative bacteria.

Gram-positive bacteria	Gram-negative bacteria
Thick layer peptidoglycan cell wall	Thin layer peptidoglycan cell wall
The outer membrane is absent	The outer membrane is present
Teichoic acid is present	Teichoic acid is absent
Porins absent	Porins present in outer membrane
Lipopolysaccharide absent	Lipopolysaccharide present
Have exotoxins	Have endotoxin + exotoxins
Stain blue or purple on Gram's staining	Stain pink or red on Gram's staining
Periplasmic space absent	Periplasmic space present

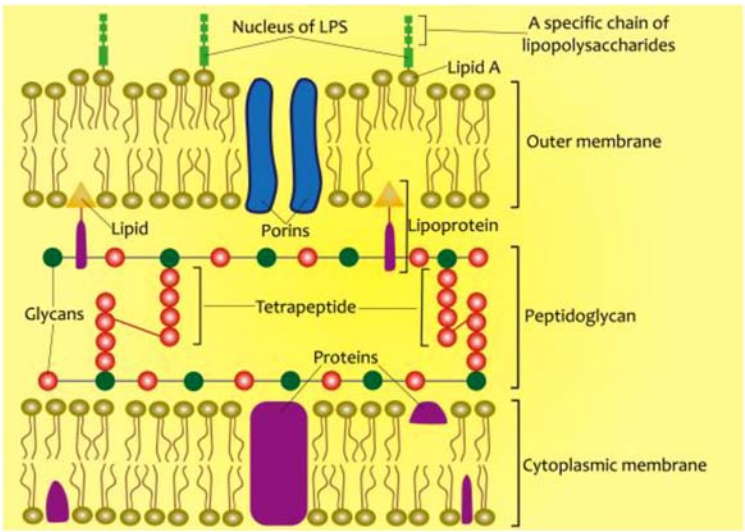

FIGURE 1.2 Cell wall of gram negative bacteria.

1.3 Classification

Endotoxin is the integral part of gm −ve bacterial outer membrane.
Exotoxin is produced by certain pathogenic gm +ve and gm −ve bacteria.

Bacteria are classified by various ways:

1) **Gram stain:** Differential method of staining bacteria and assigning them into one of two groups.
   - Gram positive (gm +ve) → stain blue or purple
   - Gram negative (gm −ve) → stain red.

Exceptions:

- Mycobacteria and Nocardia are acid-fast stains.
- Mycoplasma: no cell wall, cannot be stained
- Spirochetes: darkfield microscope, too small
- Obligate intracellular bacteria

2) **Shapes** (Fig. 1.3)

- Cocci—spherical
- Bacilli—rod shape
- Pleomorphic—no distinct shape → Chlamydia and Rickettsia
- Spiral—S-shaped or comma-shaped → Spirochetes
- Branching filamentous → Actinomyces (gm −ve anaerobic) and Nocardia
- Without cell wall → Mycoplasma

3) **Use of oxygen**

- Obligate aerobes: Require oxygen for survival. They have catalase, peroxidase, and superoxide dismutase to breakdown H_2O_2 and neutralize superoxide radical (Fig. 1.4).
- Anaerobe: Cannot survive in oxygen, and do not have any enzymes.
- Facultative anaerobe: Can live with or without oxygen. Have catalase and superoxide dismutase.
- Microaerophilic: Does not have catalase, use fermentation for energy need. Can tolerate oxygen with low concentration.

1.4 Gram staining

Bacteria are colorless and are nonvisible under a light microscope. Dyes are used to color them. Some bacteria are mostly gram positive, retain the blue dye (crystal violet), and appear blue under a microscope, while gram-negative bacteria whose outer membrane is dissolved using alcohol do not retain the blue color and take the red color of safranin dye during counterstaining.

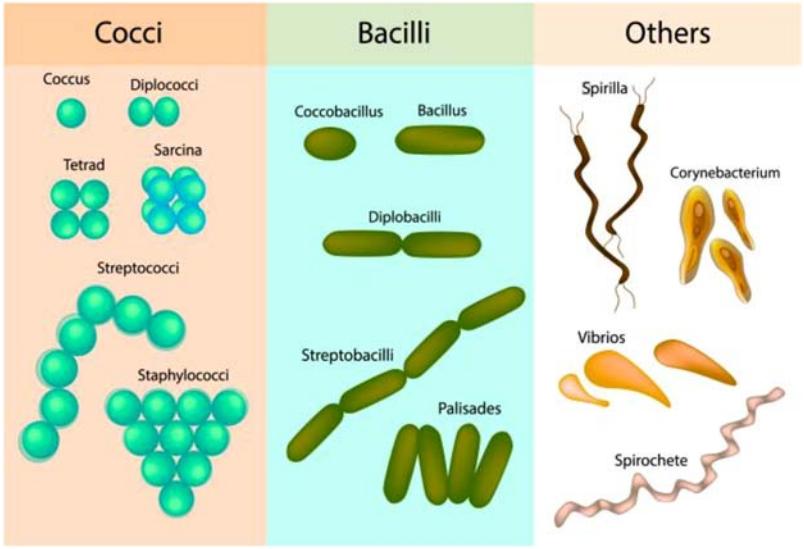

FIGURE 1.3 Shapes of bacteria.

Superoxide dismutase
$O_2^- + 2H^+ \rightarrow H_2O_2$

Catalase
$H_2O_2 \rightarrow H_2O + O_2$

Peroxidase
$H_2O_2 + NADH + H^+ \rightarrow 2H_2O +$ NAD

FIGURE 1.4 Enzymes in bacteria.

Procedure of staining usually involves several steps. First step is fixing the sample on a slide, then use crystal violet dye and wait for 1 minute and then wash off with water. This removes extra dyes from the sample. The sample is flushed with iodine solution and washed off with water and 95% alcohol. This partially dissolves the lipid outer membrane of the gram-negative bacterial cell. Counterstaining with safranin (red dye) makes the gram-negative cell look red (gray in print version) in a light microscope, while gram-positive bacteria appear blue or purple (dark gray in print version).

1.5 Bacterial pathogenicity

Bacteria are present all over the environment. Most of the bacteria are harmless and have a symbiont relation with the host. We have millions of bacteria that live peacefully in our

bodies. However, some of these bacteria become pathogenic when our immune systems decline or bacteria acquire certain structures which make them virulent.

Structures responsible for pathogenicity:

- Capsule
- Flagella
- Pilli
- Spores
- Toxins
- Biofilm
- Intracellular growth

Capsule: Capsules are usually made up of polysaccharide molecules except in *B. anthracis,* which is made up of amino acid residue. The presence of capsules in bacteria makes it more virulent because macrophages and other immune cells cannot phagocytize these bacteria. For example, *Streptococcus pneumonia, Haemophilus influenzae,* and *Neisseria meningitis*. However, capsule-specific antibiotics directed against the capsules help the immune cells to engulf or phagocytize these bacteria through opsonization.

Opsonization: It is a process in which microorganisms are coated with immunoglobulins, complement factors, or other host proteins/lipid to facilitate phagocytosis. The process can be classified into:

- Antibody-mediated opsonization: In this process, Fab region of the antibody binds to the antigen, and the Fc region of the antibody binds to the Fc receptor on the phagocytic cells and helps phagocytic cells, which include neutrophils, eosinophils, macrophages, and natural killer cells, to recognize the invading particles, and engulf and enzymatically digest them. Antibodies also activate the complement system via the classical pathway.
- Complement protein-mediated opsonization: Presence of foreign particles results in spontaneous activation of complement cascade via alternate pathway. In this pathway, complement proteins C3b, C4b, and C1q play an important role in opsonization. In the process, C3 converts to C3b which binds to invading particles and is recognized by phagocytic cells.
- Other protein-mediated opsonization: Circulating proteins such as pentraxins, collectins, and ficolins have pattern-recognition receptors (PRRs). These proteins recognize the foreign invaders and coat them to be recognized by phagocytic cells.

Flagella and pilli: Flagella and pili are protein filamentous structures, pouching like a tail from the cell membrane. Flagella are longer than pili and used for the movement of bacteria called chemotaxis. Pilli are relatively short and used for adherence.

Example: Flagella → *Escherichia coli, Vibrio cholera,* and *Proteus mirabilis*.

Pili → *Neisseria gonorrhea, Campylobacter jejuni,* and *Bordetella pertussis*.

Spores or endospores: Dormant forms of bacteria that are highly resistance to heat, cold, drying, and any other environmental changes.

Example: Bacillus species and Clostridium species.

Toxins: Toxins are protein or nonprotein molecules that are produced or part of cell wall to target host cells. Broadly classified into:

- **Exotoxin:** These are heat-sensitive soluble protein molecules released by both gram-positive and gram-negative bacteria. They are of various types and cause various pathological conditions in a human. Examples: neurotoxin, enterotoxin, and pyrogenic toxin. They are classified into three categories.
  - Type I: Binds to cell surface receptors and stimulates the cell to produce cytokines or other proinflammatory mediators, for example, superantigen binds to host's T-cell receptor (TCR) and stimulates the T cells to produce excess amount of cytokine causing massive tissue damage.
  - Type II: These toxins produce the effect by damaging the host cell membrane such as forming pores in the membrane. This results in cell lysis and death.
  - Type III: These toxins have two units—AB units. B units usually bind with the host cell membrane, and A units have enzymatic activity. Once delivered to the host cell, A unit inhibits cell functions or causes cell death. For example, toxin produced by *Clostridium tetani.*
- **Endotoxin:** Part of the outer membrane of gram-negative bacteria. Also called lipid A. It is secreted during the lysis of gram-negative bacteria and is responsible for sepsis, septic shock, bacteremia, and other conditions in human. These are heat-stable molecules.

Biofilm: Some bacteria such as *Staphylococcus epidermidis* produce polysaccharide structure similar to capsule. This helps the bacteria to attach to prosthetic devices and protect the bacteria from immune cells and antibiotics.

Intracellular organisms: Certain bacteria are intracellular where they are protected from antibodies and immune cells.

Examples: *Listeria monocytogenes*, *Salmonella typhi*, Yersinia, *Francisella tularensis,* Brucella, and Mycobacterium.

1.6 Normal flora

Mouth/oropharynx: Viridian group, Haemophilus species, Neisseria species, and anaerobes.

Small bowel: *E. coli* and anaerobes.

Colon: *E. coli*, Klebsiella species, Enterobacter, Enterococcus, and anaerobes.

Vagina: Lactobacillus species, Viridian group, Staphylococcus, gram-negative bacilli, and anaerobes.

Skin: Staphylococcus, Corynebacterium, Propionibacterium species, and Bacillus.

1.7 Manifestations of infection

Signs and symptoms of infection are broadly classified into local or systemic. Local infection usually affects the local area and does not involve the whole body. Systemic infection involves the entire body and multiple organs. However, there are some general symptoms that are usually present and considered clinical signs of infection.

1.7.1 Fever

Normal body temperature varies among individuals, sex, race, and even the time of the day. Usual normal range of body temperature is 35.3–37.7°C (95.5–99.9°F). Elevation of body temperature above 37.8°C (99.9°F) orally or >38.2°C (100.2°F) rectally is considered fever. However, not all infections increase body temperature above normal. Sometime infection such as in septic shock may result in low body temperature <95°F (35°C). Infection is the most common cause of the increase in body temperature.

Body temperature is controlled by thermoregulatory centers in the hypothalamus. Certain substances called pyrogen increase body temperature by inducing the release of cytokines (IL-1, IL-6, and TNF). These cytokines increase the synthesis of prostaglandins E2, which is an inflammatory agent and play an important role in upregulating the thermoregulatory centers. Most common bacterial pyrogens are: Endotoxins that are the component (LPS) of gram-negative bacterial cell wall, toxins secreted from gram-positive and gram-negative bacteria, viral DNA or mRNA, and bacterial or viral envelopes are all considered pyrogen and resulting in increased body temperature.

Other causes of fever:

- Autoimmune/inflammatory disease
- Cancer
- Drugs: Amphetamines, cocaine, antipsychotic, beta-lactam, sulfa drugs, and interferons

Fever with rash:

- Meningococcemia
- Rocky Mountain spotted fever
- Lyme disease
- Syphilis
- Dengue fever
- Drug hypersensitivity

1.7.2 Difference between fever and hyperthermia

Increase in body temperature in hyperthermia is different and could be fatal. Hyperthermia should be differentiated from high temperature. Heat stroke, exercise in hot environments, hyperthyroidism, use of certain drugs like ecstasy, atropine, and

certain anesthetic drugs are all examples of possible hyperthermia. In hyperthermia, body heat production is higher than heat lost. It is very important to know the signs and symptoms of hyperthermia which include:

- High body temperature
- Muscles cramp
- Nausea vomiting
- Headache, confusion, and seizure
- Sinus tachycardia
- Skin may be moist or dry
- Coma and death

1.7.3 NSAID as antipyretic agents

Synthesis of prostaglandin E2 depends on the enzyme cyclooxygenase. E2 is a strong inflammatory agent and is responsible for increased body temperature. Enzyme cyclooxygenase is required to convert arachidonic acid into inflammatory agents such as thromboxanes, prostaglandins, and prostacyclins. NSAID inhibits enzyme cyclooxygenase and indirectly prostaglandin E2.

1.7.4 Other signs of infections

Increased pulse rate, rapid breathing, respiratory alkalosis, pain, fatigue, headache, malaise, cachexia, weight loss, and loss of appetite are all signs of infection. However, these signs are not very specific to infection. Other inflammatory conditions such as autoimmune diseases, cancers, and trauma may also cause the same signs and symptoms.

1.7.5 Hematological signs of infection

Infection usually increases circulating neutrophils and other leukocytes including immature leukocytes called band cells (immature neutrophils-left shift). Other changes like morphological changes in neutrophils such as “Dohle bodies” and vacuolization, increased serum ferritin level, platelet, and erythrocytes count are common. Profound leukemia in severe infection usually has a poor prognosis. These changes can also be observed in stress, trauma, and other inflammatory process.

1.7.6 Biomarkers of infection

There has always been a search for ideal biomarkers of infection. There are some traditional biomarkers such as increased white blood cell (WBC) counts, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). However, they are not very specific for infections and are also elevated in other conditions such as trauma, cancer, autoimmune diseases, or any other inflammatory process, which result in the release of

cytokines such as IL-6, IL-1, TNF-alfa, and interferon-gamma. These pro-inflammatory mediators cause an increase in the serum proteins (acute-phase protein/reactants [APR]). The mechanism how pro-inflammatory mediators raise acute phase proteins is beyond the scope of this book.

1.7.6.1 Erythrocyte sedimentation rate (ESR)

ESR measures the rate of erythrocyte sedimentation in plasma when placed in a tube. Normal ESR for men is 1−15 mm/hour and 1−20 mm/hour for women. In case of inflammation, high levels of fibrinogen and other plasma protein adhere to the red blood cell membrane and neutralize the surface negative charges. This results in cell adherence, rouleaux formation, and increasing the sedimentation of erythrocytes.

Some causes of increase ESR are:

- Inflammation
- Infection
- Trauma
- Ischemia
- Anemia
- Increase age or female sex
- Kidney disease
- Obesity

Some causes that decrease ESR are:

- Leukocytosis
- Heart failure
- Cachexia
- Low fibrin

1.7.6.2 C-reactive proteins (CRP)

CRP is secreted by the liver in response to inflammation and is a member of the pentraxins family of proteins. CRP binds to phosphocholine molecule, which is expressed on the surface of dead cells and on some bacteria and activates the complement system. CRP also binds to the Fc receptor of phagocytic cells to stimulate phagocytosis and release of cytokines. CRP rises to many folds during inflammation and peak at 48 hours. Interferon-alpha inhibits CRP from the liver cell. Therefore, during viral infection, CRP levels remain low. Recent studies have shown that continued elevated CRP levels are a risk factor of diabetes, hypertension, and cardiovascular disease.

Other proteins that increased during inflammation and infection are:

- Serum amyloid A (SAA): Concentration rises during inflammation, similar to CRP
- Haptoglobin
- Alpha-1 antitrypsin
- Hepcidin
- Fibrinogen
- Lactic acid

There are several conditions, where one marker is elevated while the other is muted. For example, in systemic lupus erythematosus (SLE), ESR is usually elevated while CRP is not.

1.7.6.3 Procalcitonin

Procalcitonin (PCT) is an amino acid precursor of calcitonin, secreted by the parafollicular C cell of the thyroid gland. In the presence of IL-6 and TNF-alpha, transcription of the *CALC*-1 gene occurs in extra thyroid tissue, and the concentration of PCT in the blood rises many folds.

Other causes of increase in PCT are:

- Small cell lung cancer
- C-cell carcinoma of the thyroid gland
- Neuroendocrine tumors
- Cardia arrest
- Trauma
- Pancreatitis
- Rhabdomyolysis
- Intestinal surgery

Some studies suggest PCT is more specific to bacterial pneumonia. In the case of sepsis, some studies found that the sensitivity and specificity of PCT are higher than CRP, while other studies found no significant advantages over CRP. PCT may also help to differentiate bacterial infection from fungal or viral infection. Low PCT points toward fungal or viral infection, while high-level points more toward bacterial infection. It is suggested that elevated CRP in the context of low PCT may consider for nonbacterial infection or inflammation. The PCT level rises in 2–4 hours in bacterial infection and peaks in 48 hours. PCT also gets clear rapidly. The rapid drop of PCT level after the start of the antibiotic suggests correct selection; otherwise, consider switching the antibiotic or nonbacterial cause of inflammation.

In sepsis, two promising biomarkers, pentraxin 3 (PTX3) and presepsin, are under research. PTX3 is an acute-phase protein and a member of the pentraxin protein family like CRP. During inflammation, PTX3 is produced by endothelial cells, mononuclear phagocytic cells, and dendritic cells. Its main function is to help the immune cells in various ways, including activation of the complement system. Presepsin is a soluble form of CD14, expressed on the membrane of monocytes and macrophages, and is a part of the pattern recognition molecule. Presepsin is present at a low level in healthy individuals but rises to many folds in systemic bacterial infection. However, the use of these biomarkers needs further studies.

Other possible biomarkers of the future:

- Human neutrophil elastase (HNE)
- Cathepsin G
- Interleukin-6

For fungal infection, galactomannan (GM) and 1,3-beta-D-glucan (BDG) are being approved by the FDA. Both biomarkers are components of the fungal cell wall. Other possible future fungal biomarkers under investigation are:

- D-arabinitol
- Gliotoxin

No single test is an ideal test for infection. Research is continued to find an ideal biomarker.

1.8 Basic immunology

Our immune system can be divided into:

a) Innate immunity
b) Acquired immunity

1.8.1 Innate immunity

- Fast, nonspecific, and does not require any previous exposure of antigens.
- Does not have any memory cells.
- Inmate system also include physical barriers, such as skin, gut walls, cilia of the airways, mucus, sylva, tears, etc.
- Includes:
  - Phagocytic cells such as neutrophils, monocytes, and macrophages
  - Polymorphonuclear leukocytes such as eosinophils and basophils
  - Natural killer cells

1.8.1.1 How phagocytic cells kill the invaders

Immune cells have Pattern Recognition Receptors (PRRs) on their membrane, which recognize foreign invaders having pathogen-associated molecular patterns (PAMPs). PAMP includes but is not limited to several structures in bacterial or viral cells that human cells do not have, such as peptidoglycan, LPS, lipoteichoic acid in bacterial cell walls, and viral DNA or RNA. Once the bacteria or viruses enter the human body, cells of the inmate system recognize these invaders and start into action by engulfing and trapping the microbes in a vacuole called phagosome. The phagosome fuses with other vesicles lysosome and forms phagolysosome. Enzymes present in lysosome kill the bacteria inside the phagolysosome. Another way these cells kill the invaders is by oxidative burst, which is a powerful mechanism in killing the bacteria or viruses. Besides destroying the bacteria or virus, macrophages and other infected cells secret cytokines to activate other immune cells.

1.8.2 Acquired immunity

- Very specific, slow, and require priming.
- Have memory cells and produce specific antibodies against the invaders.
- Cells of acquired immunity include:
  - B-cells
  - T-cells
- Further classified into:
  - **Humoral immunity**: Include B-cell response against the invaders, which includes conversion of plasma cells and secretion of specific antibodies.
  - **Cell-mediated response**: Involve T-cells that are required to be activated by antigen-presenting cells (APCs). However, all systems have to work together for affective immune system.
- Other components of our immune system responsible for protection are:
  - Physical and chemical barriers: Skin, mucus, cilia in our upper respiratory tract, and lysozymes.
  - Complement system, acute phase reactants (APRs), and cytokines involve in both innate and acquired immunity.

1.8.3 Cells of immune system

Cells of immune system can be divided into myeloid or lymphoid progenitor cells and comprise the following.

1.8.3.1 Myeloid cells

a) Neutrophils: Polymorphonuclear cells usually 3–5 nuclear lobes. Part of innate immune response and involve in phagocytosing the microbes. Most abundant WBCs. Half-life is about 2–3 days.
b) Eosinophils: Larger cells, stain pink, and are the major source of inflammatory response and involve in eradicating parasite.
c) Basophils: These are nonphagocytes and involve in fighting against parasite. Comprise about 5% of WBC and stain blue or purple.
d) Mast cells: Nonphagocytes and granulocytes involve in inflammatory responses. The granules inside cells contain tryptase, chymase, and heparin.
e) Monocytes: Antigen Presenting Cells (APCs) and differentiate into macrophages and dendritic cells.
f) Dendritic cells: APCs, phagocytes, and release cytokines.
g) Macrophages: They are also antigen-presenting cells, phagocytes, and secrete cytokines.

1.8.3.2 Lymphoid cells

a) These cells are developed from lymphoid progenitor cells. They are abundant in lymph nodes and comprises about 18%–42% of circulating WBCs.

b) Natural killer cells: They are part of inmate system and are lymph cells. They kill the target cell such as cancer cells and infected cells. They recognize major histocompatibility complex (MHC) class I.

c) B cells: Part of the adaptive response system. About 5%−15% of lymphocytes are B cells. They develop in the bone marrow. Main functions of B cells are to present antigens to T cells, release cytokines, production of plasma and memory cells. B-cells express antigen-binding receptors that are different from T-cells. B-cell receptors can identify all sort of antigens and does not require APCs. B-cell receptors are basically an antibody that has a transmembrane part that crosses the cell membrane. Once activated, B-cells undergo to differentiate into plasma or memory cells. Plasma cells start producing antibodies. Initially, they produce IgM, but the presence of T-cells and the type of cytokines it secret result in isotype switching. There are five main types of immunoglobulins: IgM, IgG, IgD, IgA, and IgE. Plasma cells are short lived, about six weeks, while the memory B cells are long lived and respond to any subsequent infection

d) T cells: Grow in the bone marrow and migrate to the thymus for maturation. They are part of adaptive immunity. T cells express antigen-binding receptors on their membrane known as T-cell receptors (TCRs). T cells are activated when TCR interacts with APCs. Once activated, they start secreting cytokines and differentiate into cytotoxic cells (CD8+ cells) or T-helper (Th) cells. Helper cells (CD4+ T cell) bind with MHC class II molecule and involve in secreting cytokines and helping other immune cells. Cytotoxic cells (CD8+ T cells) bind with MHC class 1 molecule and are responsible for killing infected or cancerous cells. For T cell to be fully activated require a second step called costimulation. It is when CD28 on the surface of T cell binds to B7 on APCs. This two-step process activates T cells, and they start proliferation, secreting cytokines, destroying infected cells, or helping other immune cells. Clonal expansion of cytotoxic cells produces effector cells. Most of these effector cells die after the infection is over. However, few of these cells survive and change to memory cells that can provide a quick response upon subsequent infection.

1.8.4 Cytokines

Cytokines are small protein molecules that are secreted by immune and nonimmune cells for signaling or communicating with each other. There are five main types of cytokines.

1. Interleukins
2. Tumor necrosis factors (TNFs)
3. Interferons
4. Colony-stimulating factors (CSFs)
5. Transforming growth factors (TGFs)

1.8.4.1 Interleukins Table 1.2

Interleukins are released by leukocytes and nonleukocytes. They have various effects on cell development and regulation of immune response. There are about 38 interleukins.

1.8.4.2 Tumor necrosis factors: alpha and beta

- Secreted by B cells, dendritic cells, macrophages, mast cells, monocytes, NK cells, and Th cells
- Induce apoptosis to tumor cells
- Involve in inflammatory response such as increase vascular permeability, induce fever, cachexia
- Activation of macrophages
- Antiviral
- ↑secretion of cytokines
- TNF-alpha antagonists are used in the treatment of rheumatoid arthritis, psoriasis, Crohn disease, juvenile idiopathic arthritis

1.8.4.3 Interferons

- Three types:
  - Type 1 or IFN-alpha: Secreted by viral infected cells and leukocytes
    - Inhibit viral replication
    - Express MHC
    - Clinically use in the treatment of chronic hepatitis C, Kaposi sarcoma, chronic myeloid leukemia, and metastatic melanoma
  - Type 2 or IFN-beta: produce by fibroblast
    - Inhibit viral replication
    - Class 1 MHC expression
    - Clinical use in multiple sclerosis
  - IFN-gamma: secret by NK cells and cytotoxic cells
    - Inhibit viral replication
    - Class 1 and II MHC expression
    - Activate macrophages
    - Inhibit Th2 cell proliferation

1.8.4.4 Colony-stimulating factors

- Stimulate hematopoietic stem cells proliferation and differentiation
- Various type such as granulocyte-colony-stimulating factor (G-CSF)
- Macrophage colony-stimulation factor (M-CSF)
- Stem cell factor (SCF)

Table 1.2 Classification of interleukins.

Interleukins	Secreting cells	Main effects	Comments
IL−1	B cells, dendritic cells, endothelium cells, macrophages, monocytes, natural killer (NK) cells	Proliferation of B cells, increase body temperature, anorexia, increase acute-phase reactants	IL−1 monoclonal antibody is used for treatment of Juvenile idiopathic arthritis
IL−2	CD4+ helper cells	B cells proliferation, induction of activated T cells, ↑NK cells toxicity.	Treatment of metastatic renal cell carcinoma, melanoma
IL−3	T cells, NK cells, mast cells	Stimulate hematopoietic precursors, and mast cells	
IL−4	Mast cells, NK cells, T cells	Induction of Th2 cells, stimulate B-cells and mast cells proliferation, downregulation of IL-12 production	Inflammatory response against parasitic infections
IL−5	Mast cells, Th2 cells	B-cells proliferation and induction of eosinophils	Monoclonal antibodies for severe eosinophilic asthma
IL−6	Dendritic cells, fibroblast, macrophages, monocytes, Th2 cells	Differentiation of B cells to plasma cells, ↑acute-phase reactants, ↑T cells proliferation, pyrogenic	IL−6 receptor mAb is used for rheumatoid arthritis and other autoimmune disease
IL−7	Stromal cells of bone marrow and thymus	↑differentiation of lymphoid stem cells to T and B cells precursors. Activate T cells	
IL−8	Endothelial cells, macrophages, and monocytes	↑chemotaxis and activation of neutrophils	
IL−9	Th cells	Thymocyte proliferation, ↑mast cell growth	
IL−10	B cells, macrophages, monocytes, T cells	Inhibit IL-2, ↓production of class II MHC and cytokines, ↓T cells proliferation, ↑B cell proliferation.	
IL−11	Bone morrow stromal cells	↑pro-B and megakaryocyte differentiation, ↑acute-phase reactants.	
IL−12	B cells, dendritic cells, macrophages, monocytes	Th1 differentiation, proliferation of Th1 cells, CD8 T cells, enhance NK CD8 T cell cytotoxicity.	Anti-IL 12 mAb are used for plaque psoriasis and psoriatic arthritis
IL−13	Mast cells, Th2 cells	Inhibit macrophages activation, B cell proliferation, switch IgG1 and IgE	

Continued

Table 1.2 Classification of interleukins.—cont'd

Interleukins	Secreting cells	Main effects	Comments
IL−15	B cells, dendritic cells, macrophages, monocytes, NK cells, T cells	Proliferation of T, NK, and B cell ↑cytokine production and cytotoxicity of NK and CD8 T cells	
IL−16	T helper cells and T cytotoxic cells	↑CD4 T cells, monocytes, and eosinophils activity, induction of MHC class II	
IL−17	Th17 cells, gamma-delta cells, NKT cells, macrophages	↑cytokines, proinflammatory	Anti-IL 17A mAb use for ankylosing spondylitis, psoriatic arthritis, plaque psoriasis
IL−18	Monocytes, macrophages, dendritic cells	↑IFN-gamma production, ↑NK cells cytotoxicity	
IL−21	NKT cells, Th cells	↑B cells proliferation, stimulate NK cells, T cells, bone marrow precursor cells	
IL−22	NK cells, Th17 cells, gamma-delta T cells	↑acute-phase reactants, proinflammatory	
IL−23	Dendritic cells, macrophages	Induction of Th cells proliferation	mAb for the treatment of psoriatic arthritis and Crohn disease
IL−24	B cells, macrophages, monocytes, and T cells	Suppress tumor cell growth, induction of apoptosis in tumor cells	
IL−27	Dendritic cells, monocytes, macrophages	Induction of Th1 cells.	
IL−32	NK cells, T cells	Proinflammatory, T cell apoptosis	
IL−33	Endothelial cells, stromal cells, dendritic cells	Induction Th2 cytokines, cause eosinophilia	
IL−35	T cells, macrophages, dendritic cells	Suppression of inflammation	
IL−37	Macrophages and inflamed tissue	Antiinflammatory	

1.8.4.5 Transforming growth factors

- Modulate proliferation, and differentiation of cells.

1.8.4.6 Summary of cytokines

- Pro-inflammatory cytokines:
  - IL-1, IL-6, IL-12, IL-18, TNF, IFN-y

- Antiparasitic/allergy
  - IL-4, IL-5, IL-10, IL-13
- Regulate immune response
  - IL-10, TGF-beta
- Stimulate growth and differentiation
  - GM-CSF, M-CSF, IL-7
- Chemotaxis
  - IL-17, IL-8

1.9 Major histocompatibility complex

MHC is a set of genes located on chromosome 6, codes for proteins found on the surface of the cells and helps the immune system recognize self and nonself-molecules. The MHC molecules are also called human leukocyte antigens (HLA). There are two types of MHC molecules.

- Class I MHC are found in all nucleated cells except erythrocytes. MHC 1 binds with cytotoxic CD8 cells. Class 1 antigens are made up of heavy alpha chains and light chains (beta chains). The alpha chains are coded by MHC 1 gene at HLA-A, HLA-B, and HLA-C loci on chromosome 6, and beta chains are encoded on chromosome 15.
- Class II MHC is found on APCs such as macrophages, dendritic cells, monocytes, and B cells. Antigens are presented to T helper cells (CD4). Class II MHC consists of two polypeptide chains, alpha and beta. Both chains are encoded by MHC II HLA-DP, DQ, and DR on chromosome 6.
- Class III Region: Does not have any HLA gene but contains several genes of important molecules such as components of complement system C2, C4, TNF, etc.
- Some autoimmune disorders are associated with these HLA genes.
  - Reactive arthritis and ankylosing spondylitis are associated with HLA-B27
  - Multiple sclerosis is linked to HLA-DR2
  - Rheumatoid arthritis to HLA-DR4
  - Association of HLA-B*15:2 with carbamazepine related Steven Johnson syndrome in southeast Asian population.

1.10 Complement system

Groups of several protein molecules synthesize in the liver and play an important role in the fight against the infection. The complement system is divided into:

a) Classical pathway
b) Alternate pathway
c) Lectin binding pathway

1.10.1 Classical pathway

The classical pathway comprises protein molecules labeled C1 to C9 and is activated when C1 interacts with the antigen-IgM or antigen-IgG complex. Once activated, it cleaves other proteins.

1.10.2 Alternate pathway

This pathway does not require interaction with antibodies. Instead, it is activated when a component of the bacterial or viral cell membrane or cell wall comes in contact with C3 protein, cleaves and activate it.

1.10.3 Lectin pathway

Activated when mannose-binding protein bind to mannose, fucose, or N-acetylglucosamine, a common molecule on several bacterial, viral, or yeast cell walls.

All three pathways start a little bit differently but end the same way. In the final common pathway, C3 convertase cleaves C3 into C3a and C3b and results in the formation of membrane attack complex (MAC). MAC is cytotoxic and creates a hole in foreign cells. In addition, C3b acts as an opsonin by coating the microorganism. C5a and C3a also act as chemotaxis and recruit neutrophils, eosinophils, and monocytes at the site of inflammation and help basophils and mast cells to degranulate.

Various other proteins regulate these pathways to prevent out-of-control responses. For example, the classical pathway is regulated by C1 inhibitor, and the alternate pathway is by properdin, factor H, and decay-accelerating factor.

1.11 Identification of microorganisms

Several laboratory tests are used to identify and susceptibility of the microorganism.

1. Microscopic exam
2. Culture
3. Susceptibility tests
4. Immunologic tests
5. Nucleic acid-based identification
6. Nonnucleic based identification

1.11.1 Microscopic examination

Most bacteria can be visualized under a microscope. Several factors, such as the quality of the sample, type of stain required, microorganism, and microbial load, play an important role in visualizing the bacteria under the microscope. A microscopic exam is usually the first test used for the identification of the microorganism. Bacteria are

colorless; therefore, staining is required to see these microbes under the microscope. Most common staining method is gram staining. Other types of staining are used depending on what we are looking for. Gram staining method is discussed earlier in the chapter. A brief description of other types of staining is as follows:

a) Acid-fast stain: This type of staining is used for:

- Mycobacterium species
- Nocardia species
- Rhodococcus
- Oocytes of cryptosporidium, microsporidia, cystoisospora, and cyclospors.

These bacteria have high lipid contents in their cell wall. They retain the color of the initial dye carbol fuschin even after using the decoloring agent (alcohol). As a result, acid-fast bacteria appear red while nonacid fast bacteria appear blue with counter-staining with methylene blue.

b) Fluorescent stains:

The staining procedure uses a fluorescent dye to fluoresce the sample upon irradiation with UV light. There are two types of methods.

- Fluorochroming: Uses direct fluorescent dye, and cell culture is observed under a microscope. The dye enhances contrast and amplifies the observation about tenfold.
- Immunofluorescence: Fluorescent dyes are linked to specific antibodies to identify the bacteria. For example, Pneumocystis and legionella species.

c) Wet Mounts:

A wet mount is a common technique used in the laboratory for the observation of fungi cells, trichomonas, parasite, parasite eggs, cysts, oocytes, Treponema species, and stool samples. The samples are not stained and are observed under dark field microscopy.

d) India Ink stain:

Stain is used to visualize Cryptococcus neoformans and encapsulated fungi. The background is stained, and the organism appears as a halo.

e) Warthin–Starry stain:

Silver nitrate-based staining. It is used to visualize spirochetes, *H. pylori*, Microsporidia, and *Bartonella henselae*.

f) Wright and Giemsa stain:

These are two types of staining and are used for detecting.

- Parasite in blood, such as malarial parasite. Giemsa stain is used in both thick and thin smears, while Wright stain is used only in thin smears.
- Giemsa stain composes of Azure B, methylene Blue, and eosin dye. Wright stain use only methylene blue and eosin dye.
- Giemsa stain can be used in staining chromosomal aberration. Wright stain is used to differentiate blood cell types.
- Detect *Histoplasma capsulatum* in phagocytes and tissue cells.
- Intracellular bacteria.
- Pneumocystis jirovecii.

1.11.2 Culture

It is a method of growing microbes in nutritional media under controlled laboratory conditions. It is used to identify microbes and can also be used for antimicrobial susceptibility.

There are several methods used to grow microorganisms in a lab.

1.11.2.1 Broth culture

It is a liquid media. Sterile nutritional liquid broth such as tryptic soy broth or brain-heart broth is used and is inoculated with the bacteria and placed in an incubator for 24–48 hours to grow the microorganism. This kind of culture is usually used for fast-growing bacteria. Note the differences in the dispersion pattern in aerobic and anaerobic or facultative anaerobic bacteria in the media.

- Facultative anaerobic bacteria evenly dispersed in the media.
- Obligate anaerobic bacteria clumps together at the bottom.
- Obligate aerobic bacteria form a layer at the top.
- Broth cultures are used to grow a large number of microbes

1.11.2.2 Agar plates

This includes agar-based culture in Petri dishes of various sizes. Easy to manipulate the sample and isolate the desired strain of bacteria. Different types of agar plates are available, such as blood agar, chocolate agar plate, Thayer–Martin agar, etc.

- Blood agar media: Contain mammalian blood and use to detect hemolytic activities of streptococcus bacteria.
- Chocolate agar: blood lysis and heated at 80°C. No actual chocolate. Named because of the color. Use for *H. influenzae*.
- Thayer–Martin agar: *N. gonorrhea*.
- Bile esculin agar: Enterococci and group D streptococcus.

- MacConkey agar: inhibit gram-positive bacteria. Use to differentiate gram-negative bacteria.
- Several other types of agar plates are available for the growth of specific bacteria.
- Virus cultures are obtained from their appropriate eukaryotic cells. Specimens are inoculated in tissue culture that supports the growth of particular virus. Media contain anti-bacterial and antifungal agents to inhibit the growth of other microbes. Not all viruses can be identified through the culture method. Some require other methods to be identified. For example:
  - Epstein–Barr virus, hepatitis B virus, hepatitis E virus, and HIV require enzyme immunoassay.
  - Hepatitis A and hepatitis D viruses require serological tests
  - HIV, influenza virus, respiratory syncytial virus, and SARS-CoV2 require nucleic acid-based methods.

1.11.3 Susceptibility test

The susceptibility tests determine the effectiveness of an antimicrobial agent against particular microbes. There are different methods used to achieve the goal.

- Quantitative methods
- Semiquantitative methods
- Nucleic acid-based methods.

a. Quantitative Methods:

This method uses the disk diffusion method (Kirby–Bauer test). It is best for the rapid-growing bacteria. Antibiotic impregnated disks are placed on an agar plate, and the zone of inhibition is measured after 16–18 hours. Results are reported as:

- Susceptible (S)
- Intermediate (I)
- Resistant (R)

The method is low-cost and flexible in the choice of antimicrobial agents.

b. Semiquantitative Methods:

Based on the minimum inhibitory drug concentration (MIC) required to inhibit the specific microorganism. Results are translated to sensitive (S), Intermediate (I), and resistant (R).

c. Nucleic-acid-based methods: Based on identifying resistance genes.

1.11.4 Immunologic tests

Based on detecting antigens and antibodies.

- Agglutination tests
- Complement fixation tests

- Enzyme immunoassays tests
- Precipitation tests
- Western blot tests

a. **Agglutination tests (ATs):** In AT test, antigens or antibodies are coupled with small particles such as latex beads or gelatin particles and mixed with the specimen. If the target antibodies or antigens are present in the sample, it causes agglutination, which can be measured. The test is fast but is not very sensitive.
b. **Complement fixation (CF):** In this test, a known quantity of complement and antigen with the specimen is incubated. The degree of complement fixation corresponds to the relative quantity of antibodies in the specimen. The test is used to measure IgM and IgG antibody titers and is used for the diagnosis of viral and fungal infections, specially coccidioidomycosis.
c. **Enzyme Immunoassays (EIAs):** Also called Enzyme-linked Immunosorbent assay (ELISA), is a test with high sensitivity and is usually used for screening. The test detects specific antibodies or antigens by producing an enzyme-linked color change. The test can be used for the following infections:
   - HIV
   - Lyme disease
   - Rocky Mountain spotted fever
   - Rotavirus
   - Syphilis
   - Toxoplasmosis
   - Varicella-zoster virus
   - Zika virus
d. **Precipitation tests**: Low sensitivity, measure precipitation of antigen and antibody complexes. Use to detect fungal infection.
e. **Western blot test** detects a specific protein in a sample. The protein sample is run on a gel, sorted out according to molecular size, and marked the targeted protein using monoclonal specific antibodies to visualize. Western blot has a high specificity and is usually used as a confirmatory test. However, it is no longer used as a confirmatory test for HIV.

1.11.5 Nucleic acid base identification

This method is based on the identification of DNA or RNA sequences and is highly sensitive and specific. This method can be used in any type of microorganism. To use this method high concentration of microorganism or nucleic acid amplification is required. In nucleic acid amplification, minute amount of DNA or RNA is replicated many times to achieve the require amount. PCR and RT-PCR are commonly used for the target amplification.

1.11.6 Nonnucleic acid base identification

Bacteria can be identified manually by looking the culture and observe the bacteria under microscope after suitable staining. Some scientists use special methods such as chromatography and mass spectroscopy to identify the microorganism.

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2

Gram-positive bacteria

2.0 General Description

- Stains blue or purple in Gram stain
- Thick peptidoglycan cell wall made of repeated disaccharides (N-acetyl glucosamine) and four amino acid side chains
- Each side chain is connected with each other by cross-linking, catalyzed by the enzyme transpeptidase (penicillin-binding protein)
- Antibiotic penicillin binds to transpeptidase and inhibits the cell wall synthesis
- Cell wall of Gram-positive bacteria is thick as compared to Gram-negative bacteria and has a polysaccharide teichoic acid, which acts as an antigen
- No endotoxin except Listeria
- Some species secrete exotoxin
- Gram-positive bacteria comprise cocci, bacilli, and branching filaments

  Some members are spore forming.

- According to the Surveillance and Control of Pathogen of Epidemiologic Importance (SCOPE), Gram-positive bacteria caused more blood stream infection (~76%) than Gram-negative bacteria (~22%) in 2000; this trend is increasing

Infectious Diseases. https://doi.org/10.1016/B978-0-443-18742-1.00260-8
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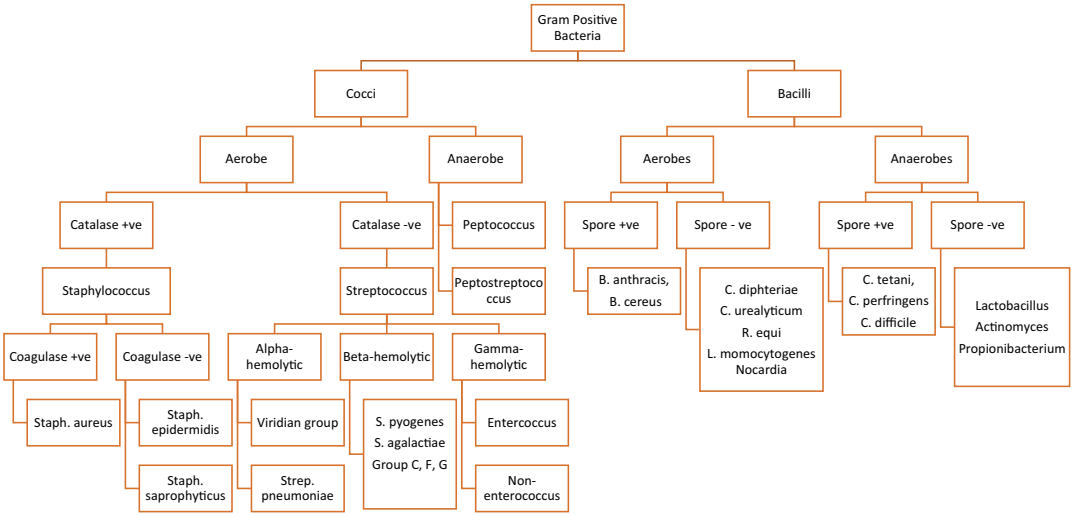
2.1 Classification of Gram-positive bacteria



2.2 Gram-positive cocci

A) Aerobic/facultative anaerobic
- **A-1)** Staphylococcus
- **A-2)** Streptococcus

B) Anaerobic
- **B-1)** Peptococcus
- **B-2)** Peptostreptococcus

2.2.1 Staphylococcus

- Cocci in clusters
- Catalase positive → differentiates it from Streptococcus and Enterococcus species, which are catalase negative
- Includes:
  1) *Staphylococcus aureus*
  2) *Staphylococcus epidermidis or Staph. epidermidis*
  3) *Staphylococcus saprophyticus*

2.2.1.1 Staphylococcus aureus

- Catalase positive
- Coagulase positive → differentiates it from *Staph. epidermidis* and *Staph. saprophyticus,* which are coagulase negative

Virulence factors:

- Coagulase → converts fibrinogen to fibrin and forms a protecting layer around bacteria
- Catalase → breakdowns H_2O_2 into oxygen and water → $2H_2O_2 \rightarrow 2H_2O + O_2$
- Protein A → binds to Fc portion of IgG antibody and protects the bacteria from opsonization and phagocytosis
- Penicillinase → inactivates beta-lactam antibiotics
- Lytic enzymes → hyaluronidase, lipase, and protease; destroys or breakdowns tissue proteins, proteoglycans, fats, etc.
- Exotoxin → causes scalded skin syndrome
- Enterotoxins → cause food poisoning
- Toxic shock syndrome toxin: TSST → superantigen

About 20% of population is carriers of *Staph. aureus* in their nose, skin, axilla, etc.
Treatment is recommended for hospitalized or surgical patients.
Bactroban is the drug of choice for the treatment; regrowth is common.

Clinical significance:

- Bacteremia
- Acute bacterial endocarditis (ABE): number 1 cause in IV drug users and usually infects the tricuspid valve
- Meningitis
- Brain abscesses
- Lactational mastitis
- Pneumonia → broncho pneumonia (lobular)
- Skin and soft tissue infection
- Septic arthritis
- Nosocomial wound infection → most common cause
- Osteomyelitis
- Urinary tract infection
- Food poisoning → enterotoxin → heat stable and short incubation period (meats, mayonnaise, and custard are the common sources of infection)

- Scalded skin syndrome → Exfoliative toxins A and B
- Toxic shock syndrome
- **Choice of antibiotics**: selection of the antibiotics depends on type of Staphylococcus involved
  - **a)** Methicillin-susceptible *Staphylococcus aureus* (MSSA)
  - **b)** Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - **c)** Vancomycin intermediate resistant *Staphylococcus aureus* (VISA)
  - **d)** Vancomycin-resistant—*Staphylococcus aureus* (VRSA)
    - **a)** MSSA
      - First choice:
        - ➢ Nafcillin, oxacillin, and cephalosporin, except ceftazidime
      - Second choice:
        - ➢ Carbapenem, tetracycline, clindamycin, chloramphenicol, sulfonamide, vancomycin, linezolid, daptomycin, and tigecycline
        - ➢ Oral: dicloxacillin, sulfamethoxazole and trimethoprim (SMZ-TMP), and linezolid
    - **b)** MRSA:
      - First choice:
        - ➢ Vancomycin, linezolid, and daptomycin
      - Second choice:
        - ➢ Ceftaroline, tigecycline, and chloramphenicol
      - VISA and VRSA:
        - ➢ Daptomycin, linezolid, ceftaroline, tigecycline, and chloramphenicol

2.2.1.2 Staphylococcus epidermidis

- Gram-positive cocci in clusters
- Facultative anaerobe
- Catalase positive
- Coagulase negative
- Urease positive
- Novobiocin sensitive
- Part of normal skin flora
- **Virulence factors:**
  - Formation of biofilms
  - Presence of genetic codes for antibiotic resistance
  - Production of hemolysin, DNase, protease, and fibrinolysin
- **Clinical significance:**
  - Causes infection in an intravascular prosthetic device, prosthetic joints, bacteremia/sepsis, endocarditis, and UTI
  - Number 1 cause of prosthetic valve endocarditis and infections due to prosthetic devices and catheters
  - Most common cause of contaminating the blood samples
  - Bacteria form a biofilm around it, which protects the bacteria from immune cells and antibiotics

- **Choice of antibiotics:**
  - Same as for *Staph. aureus* but unpredictable results due to high resistance to many antibiotics
  - Choice should be based on in vitro sensitivity testing
  - Oral therapy → rifampin + TMP-SMX or fluoroquinolone

2.2.1.3 Staphylococcus saprophyticus

- Catalase positive and coagulase negative, urease positive, and novobiocin resistant
- Second most common cause of uncomplicated UTI (*Escherichia coli* is number 1 cause)
- Does not reduce nitrate, while *E. coli* does
- Produces urease, which dissociates urea into carbon dioxide and ammonia, ↑ urinary PH, and complexes with magnesium to form urinary stones called struvite (magnesium ammonium sulfate stone)
- **Choice of antibiotics**
  - First choice:
    - ➢ Trimethoprim-sulfamethoxazole and cephalosporin except ceftazidime
  - Second choice:
    - ➢ Nitrofurantoin, levofloxacin, and amoxicillin-clavulanate

2.2.2 Streptococcus

- Organized in pairs or chains
- Catalase negative

2.2.2.1 Classification

- Beta-hemolytic group: causes complete lysis of RBC
- Alpha-hemolytic group: causes partially lysis of RBC
- Gamma-hemolytic group: does not cause RBC lysis

Streptococcus can also be classified on the basis of antigen C (carbohydrate) present on the cell wall called Lancefield antigen. There are more than 50 types, but five are important and cause diseases in humans. They are grouped A, B, C, D, F, and G.

2.2.2.2 Beta-hemolytic group

It includes Lancefield group A, B, C, F, and G.
(A = *S. pyogenes*, B = *S. agalactiae*, C = *S. equi*, F, G = *S. dysgalactiae*).

2.2.2.2.1 Group A → *Streptococcus pyogenes* (pus forming)

- Parts of normal flora of mouth, teeth, skin, and vagina
- Bacitracin sensitive and catalase negative
- **Virulence factors:**
  - Capsule

  - Toxins → hyaluronidase, streptolysin O and S, pyrogenic exotoxins, and exotoxin A and C
  - M protein → responsible for inhibiting opsonization
  - Streptokinase → converts plasminogen to plasmin
  - Lipoteichoic acid, protein F → responsible for attachment of the bacteria to host cells
- **Clinical significance:**
  - Strep throat
  - Dental infection
  - Skin infections, impetigo, erysipelas, cellulitis, and necrotizing fasciitis
  - **Scarlet fever** → starts with fever, sore throat, strawberry tongue, and rashes on trunk, which spread all over the body and feel like rough sandpaper; symptoms last for 2–5 days (Fig. 2.1)
  - Streptococcal toxic shock syndrome
- **Postinfectious sequelae**

FIGURE 2.1 Strawberry tongue (scarlet fever).

Rheumatic fever (RF)

- RF is a postinfectious sequela after strep throat but not after skin infection; there are about 3% chances in the untreated population that they may develop acute rheumatic fever
- RF is an autoimmune, antibody-mediated (against M antigen) disorder that cross-reacts with hosts' own tissue
- Sign and symptoms:
  - Migratory polyarthritis: usually involves large joints
  - Pancarditis (endocarditis, myocarditis, and pericarditis): most commonly, mitral valves are affected; mitral regurgitation is the most common manifestation of mitral valve involvement
  - Subcutaneous nodules: small painless lesions usually fade away after a week or a month
  - Erythema marginatum: pink or red nonpruritic rashes involving the trunk and sometimes limbs; face is not involved

  - Sydenham chorea: neurological disorder resulting in abrupt, nonrhythmic, involuntary movements of muscles; head, face, and tongue are commonly involved; takes about a few months to 8 or 9 months after strep infection; chorea is usually more pronounced on one side and fully resolved in 6–8 months; it disappears during sleep; may result in transient psychosis
- Risk factors:
  - Asian and Pacific islander
  - Family history of rheumatic fever
  - D8/17 B cell antigen positivity
  - Genetic susceptibility
  - Age 5–15 years
  - Low socioeconomic status
- Diagnosis:
  - Revised Jones criteria (Table 2.1)
  - Lab confirmation of strep infection plus 2 major or 1 major and 2 minor or 3 minor criteria for the diagnostic
  - Rapid strep test
  - Culture → definitive diagnosis
  - Antistreptolysin O
- Choice of antibiotics:
  - First choice:
    - Penicillin G, cephalosporin, penicillin VK
  - Second choice:
    - Azithromycin, vancomycin, clindamycin, azithromycin, and carbapenem

Poststreptococcal glomerulonephritis (PSGN)

- May occur one or 2 weeks after the initial infection of either strep throat or skin infection
- Caused by nephritogenic strain of group A strep
- Exact pathophysiology of PSGN is unknown; however, the disease is immunological in nature and type III hypersensitivity reaction; it is suggested that it results from the deposition of immune complex or antigen–antibody complex in glomeruli, which results in activation of the alternate complement pathway causing infiltration of immune cells and leading to kidney failure
- Sign and symptoms:

Table 2.1 Revised Jones criteria.

Major criteria	Minor criteria
Carditis	Mono-arthralgia
Mono or polyarthritis	Fever > 100.4°F
Chorea	↑Erythrocyte sedimentation rate
Erythema marginatum	Prolong PR interval
Subcutaneous nodules	

  - Facial and orbital edema, especially in the morning after arising from bed
  - Hypertension
  - Proteinuria
  - Dark urine due to hematuria
  - Weakness, lethargy, and generalized weakness
- Diagnosis:
  - History and evidence of strep infection → Antistreptolysin titer (ASO) and measuring other antibodies such as anti-DNAse B, antihyaluronidase (AHase)
  - Serum complement level C3, which is usually low
  - Urine analysis
  - Renal function tests
  - Kidney biopsy (rarely indicated)
- Treatment:
  - First choice:
    - Penicillin G, cephalexin, and penicillin VK
  - Second choice:
    - Azithromycin, vancomycin, clindamycin, and azithromycin
  - Antihypertensive agents
  - Diuretics
  - Dialysis if needed

2.2.2.2.2 Group B → *Streptococcus agalactiae*

- Encapsulated, group B streptococcus (GBS) colonizes human genitals, gastrointestinal tract, and upper respiratory tract of young babies
- About 30% women carry it vaginally and infect the babies during delivery
- **Virulence factors:**
  - Complex polysaccharide capsule: protects the bacteria from phagocytosis by the host's immune cells
  - Lipoteichoic acid: present in most Gram-positive bacteria; helps the bacteria in attachment with host cells
  - Hyaluronate lyase: degrades hyaluronic acid and destroys normal tissue, promoting bacterial dissemination

B for babies = cause infection in babies and mother

- **Clinical significance:**
  - Meningitis, sepsis, and pneumonia in newborn babies
  - It also causes stillbirth or spontaneous abortion
  - In postpartum women, it causes endometritis, bacteremia, sepsis, meningitis, septic arthritis UTI, and cellulitis
  - Skin infection, endocarditis, UTI, and pneumonia are uncommon but may be life threatening in immunocompromised and patients with debilitating conditions

- Diagnosis:
  - Gram stain
  - Culture
  - CAMP test: the test is used to distinguish *Streptococcus agalactiae* from other species of beta-hemolytic Streptococcus; *Strep. agalactiae* and some other bacteria produce diffusible extracellular hemolytic heat-stable protein called CAMP factor; CAMP factor acts synergistically with the beta-lysin of *Staphylococcus aureus* and results in enhanced lysis of red blood cells
  - Latex agglutination test: see Chapter 1
  - Hippurate hydrolysis test: certain bacteria, such as group B streptococci, *Gardnerella vaginalis*, *Campylobacter jejuni*, and *Listeria monocytogenes,* carry hippuricase enzyme, which hydrolyzes hippurate into glycine and benzoic acid; glycine is detected by oxidation with ninhydrin reagents and gives deep purple color; test is used to identify these bacteria
- **Choice of antibiotics:**
  - First choice:
    - Penicillin, ampicillin, and cefazolin
  - Second choice:
    - Ceftriaxone, clindamycin, and vancomycin
  - Prophylactically, 2 g of ampicillin are given 2 hours before delivery for women who tested positive

2.2.2.2.3 Group C, F, and G

- Includes: *Streptococcus dysgalactiae* and sub-specie *Streptococcus equisimilis*
- Not very common
- Associated with some cases of pharyngitis, tonsillitis in immunocompromised patients or patients with other underlying diseases
- **Choice of antibiotics:**
  - First choice: penicillin G and cephalosporin
  - Second choice: azithromycin, vancomycin, and clindamycin

2.2.2.3 Alpha hemolytic group

- Partially hemolyzes the blood agar
- Forms green color colony
- No Lancefield groups
- Includes:
  a) Viridans streptococcus group
  b) Streptococcus pneumonia

2.2.2.3.1 Viridans streptococcus group

- Very large group: includes following groups:
  - S. *mutans*
  - *S. milleri*
  - *S. mitis*

  - *S. sanguinis*
  - *S. parasanguinis*
  - *S. salivarius*
- Residents of mouth, teeth, and oropharynx
- Virulence factors:
  - Production of dextran → facilitates fibrin platelet aggregates to damaged heart valves
  - Biofilms → assist in forming dental plaque
  - Acid production → causes dental caries
- **Clinical significance:**
  - Dental infections and dental caries
  - Subacute endocarditis → most common cause
  - Associated with abscesses in various organs
  - Dental work → endocarditis → Viridians streptococcus
- **Risk factors:**
  - Immunocompromised patients
  - Dental disease
- **Choice of antibiotics:**
  - First choice: penicillin, ampicillin, ceftriaxone, and vancomycin
  - Second choice: linezolid, clindamycin, and cephalosporin

2.2.2.3.2 *Streptococcus pneumoniae*

- Gram positive, alpha-hemolytic, diplococci, lancet-shaped bacteria in chains or pairs
- Lysis by bile and optochin sensitive
- There are more than 90 serotypes, but few cause serious infections

Risk factors:

- Age <2 or >65 years
- Chronic illness
- Immunodeficiency
- Asplenic patient
- Sickle cell disease
- Smokers
- Residents of convalescent home
- Alaskan native, Aborigines, and American Indian

Virulence factors:

- Capsule
- Adherence protein
- Biofilm formation
- Pneumolysin toxin

Clinical significance:

- Pneumonia (lobular)
- Otitis media in children
- Meningitis
- Septic arthritis
- Pneumococcal endocarditis

- **Choice of antibiotics:**
  - First choice: penicillin G or VK, ceftriaxone, levofloxacin, moxifloxacin, vancomycin
  - Second choice: clindamycin, linezolid, ceftaroline, cefepime, doxycycline, amoxicillin-clavulanate
- Vaccine:
  - PPV 23 → for adults; low immunity
  - PCV 13 → for children and seniors; high immunity; covers >90% serotypes

2.2.2.4 Gamma hemolytic group

- Does not cause any hemolysis on blood agar; comprises:
  a) Enterococcus
  b) Nonenterococcus

2.2.2.4.1 Enterococcus

- Includes:*Enterococci faecalis* and *E. faecium*
- Formerly belongs to Group D Streptococcus, reclassified
- Normal flora of the intestine
- Can survive in high salt concentration at 10–40°C and high pH for 30–60 minutes
- **Virulence factors:**
  - Intrinsic resistance to antibiotics
  - Adheres to heart valves
  - Lipoteichoic acid
  - Extracellular superoxide production
  - Lytic enzymes, gelatinase and hyaluronidase
- **Clinical significance:**
  - Hospital-acquired urinary tract infection
  - Wound infection
  - Prosthetic valve endocarditis
  - Infection of IV catheters → sepsis/bacteremia
- **Choice of antibiotics:**
  - Resistance to most antibiotics: Especially *E. faecium* is resistant to ampicillin, vancomycin, and aminoglycoside
  - For penicillin-sensitive strain → penicillin G and ampicillin

- For penicillin-resistant strain → vancomycin
- For vancomycin-resistant strain → daptomycin + ampicillin or ceftriaxone or ceftaroline
- Linezolid
- Nitrofurantoin or fosfomycin for cystitis

2.2.2.4.2 Nonenterococcus

- Includes → *S. bovis* (*S. gallolyticus*) and *S. equinus;* still a part of streptococcus classification group D
- Causes endocarditis and biliary tract infections
- Antibiotics:
  - First choice: Penicillin G
  - Ceftriaxone ± gentamicin
  - Second choice: vancomycin ± gentamicin

B) Anaerobic Gram-positive cocci → see Chapter 3

2.3 Gram-positive bacilli

2.3.1 Classification

a) Aerobic
b) Anaerobic
  a) Aerobic or facultative anaerobic Gram-positive bacilli can further be classified into
    i) Spore forming
    ii) Non-spore forming

2.3.2 Spore-forming Gram-positive bacilli

- *Bacillus anthracis*
- *B. cereus*

2.3.2.1 Bacillus anthracis

- Rod shape bacteria causing anthrax, a zoonotic disease, and usually infects animals but occasionally can be transferred to humans
- Word anthrax is a Greek word meaning coal, which refers to a dark color of skin eschars it causes
- Spore-forming bacteria survive in a wide variety of environments and a wide range of temperatures
- **Virulence factors:**
  - Capsule: helps the bacteria escape from phagocytic cells

- Toxin: edema toxin and lethal toxin; edema toxin causes massive local edema, while lethal toxin stimulates the massive release of cytokines from macrophages, which is responsible for sudden death in the infected person
- Rapid replication

- **Clinical significance:**
  - Responsible for anthrax

Anthrax

- Anthrax usually occurs in domestic animals such as cows, goats, and horses;humans are infected when exposed to infected animals or their products; anthrax can be classified into the following types:
- Cutaneous anthrax (90%): → www.images.google.com
  - Acquired by contact with infected animals and contaminated soil or other products
  - Incubation period is usually 2–3 days but may take up to 2 weeks
  - It usually starts with a painless, pruritic, red or brown papule followed by a necrotic ulcer with a black depressed eschar with edema around it
  - Local lymphadenopathy, fever, headache, nausea, and vomiting are common
  - Untreated cases may develop into septicemia with a high mortality rate (Fig. 2.2)

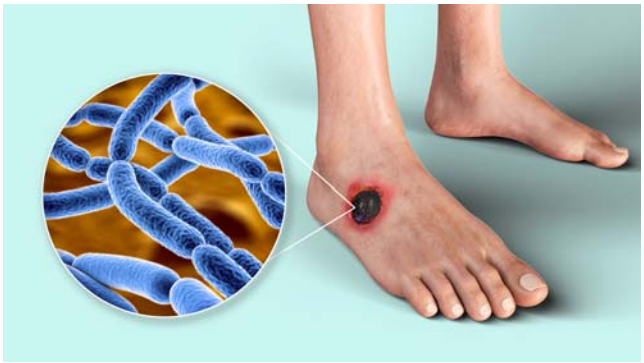


FIGURE 2.2 Cutaneous anthrax.

- Pulmonary anthrax:
  - Usually due to inhalation of the spores and accounts for about 2%–5% of all anthrax cases
  - It starts with flu-like symptoms that progress to severe respiratory distress and results in shock, cyanosis, pulmonary edema, and coma; mediastinum widening due to mediastinitis is the classical finding in a chest X-ray

- Gastrointestinal (GI) anthrax:
  - Consumption of undercook meat of infected animals
  - GI anthrax can be classified into abdominal or oro-esophageal form
  - In abdominal form, usual symptoms are abdominal pain, nausea, vomiting, diarrhea with or without blood, abdominal swelling, intestinal necrosis, and septicemia
  - In case of oro-esophageal form, usual symptoms associated are sore throat, dysphagia, fever, and edema
- Meningitis: any of the above anthrax cases may result in hemorrhagic meningitis, which, in most cases, may result in death in 24 hours with overall survival is only 6%
- Diagnosis:
  - Clinical
  - Gram stain and culture
  - Polymerase chain reaction (PCR)
  - Chest X-ray → unexplained mediastinal widening and pleural effusion
- Antibiotics:
  - First choice
    - Ciprofloxacin
    - Penicillin or ampicillin
  - Second choice
    - Levofloxacin
    - Doxycycline
    - Clindamycin
- For pulmonary anthrax, add raxibacumab or obiltoxaximab or anthrax immune globulin
- Prevention:
  - Proper hygiene and protection from infected animals
  - Active immunization in high-risk patients
  - BioThrax is the Food and Drug Administration (FDA)-approved toxin base vaccine

2.3.2.2 Bacillus cereus

- Spore-forming, Gram-positive bacilli isolated from soil, vegetables, milk, fried rice, cooked poultry, meat, soup, fruits, mashed potatoes, and vending machine items
- It is also found in the gut flora of invertebrates
- Gastroenteritis, caused by the production of enterotoxins
- **Virulence factors:**
  - There are two types of enterotoxin
  - Heat-stable: manifested by nausea, vomiting, abdominal cramp, and rarely diarrhea; it is self-limiting; usually, by consumption of contaminated rice where heat-stable toxin is not destroyed; incubation time is 1–6 hours

  - Heat-labile: usually causes profuse watery diarrhea and abdominal cramps it stimulates adenylate cyclase-cyclic adenosine monophosphate in intestinal epithelial cells; it results from ingestion of contaminated meat and vegetables it has longer incubation time
- **Clinical significance**: associated with
  - Food poisoning
  - Posttraumatic ophthalmitis
- Symptoms start within 6–15 hours after consuming the contaminated food
- Lasts about 24 hours, and people recover without any treatment
- Rarely causes opportunistic infections, such as bacteremia, toxin-induced liver failure, and posttraumatic eye infection
- *B. cereus* eye infection results in rapid eye destruction and usually occurs after eye injury with a contaminated object
- Antibiotics:
  - No antibiotics are needed for food poisoning as it is an enterotoxin
  - IV fluid and symptomatic treatments
  - For bacteremia, first choice is vancomycin
  - second choice is fluoroquinolone or imipenem
  - Resistance to most beta-lactam except carbapenem
  - ±Clindamycin → check the sensitivity
  - For invasive disease use: clindamycin, erythromycin, aminoglycoside, and tetracycline

2.3.3 Non-spore-forming Gram-positive bacilli

- *Corynebacterium diphtheriae*
- *Corynebacterium* urealyticum
- *L. monocytogenes*
- Nocardia

2.3.3.1 Corynebacterium diphtheriae

- Club-shaped, non-spore-forming, Gram-positive bacteria with metachromatic granules; when cluster together seems to be arranged in characteristic pattern resemble like a Chinese letters
- Not all *C. diphtheriae* are pathogenic or secrete diphtheria toxin
- **Virulence factors:**
  - They become pathogenic when invaded by bacteriophages, which contain tox-gene, code for diphtheria toxin
  - Diphtheria toxin has two subunits, which are joined together by the disulfide bond

    - Subunit A
    - Subunit B
  - Subunit B is used for attachment with host cell membrane, while subunit A interferes with cell protein synthesis and result in cell death
- Clinical significance:
  - Responsible for diphtheria

Diphtheria

- Classified into pharyngeal or cutaneous diphtheria
- Pharyngeal diphtheria:
  - Caused by toxin producing strain
  - Symptoms start with sore throat, fever, nausea, and croupy cough
  - Characteristic dirty gray, fibrinous pseudo-membrane around tonsillar area, which bleeds if scraped
  - The membrane may block airway and cause complete obstruction
  - Neck edema and enlargement of cervical lymph nodes, causing swollen neck (bull neck)
  - Absorbed toxin may cause severe prostration, stupor, coma, or death
  - If untreated, diphtheria toxin may reach to distant organs and cause myocarditis, arrhythmias, neuritis, and acute tubular necrosis

www.images.google.com
type pharyngeal or cutaneous diphtheria to see the images.

- Cutaneous diphtheria:
  - Similar to chronic skin conditions such as eczema and psoriasis, usually on extremities; may look like punch out ulcers
- Risk factors:
    - Unvaccinated people
    - Exposure to infected people
    - Travel to endemic area
    - Age group <15 years or >25 years
  - Transmission:
    - Respiratory drops
    - Contact of nasopharyngeal secretion
    - Contact with skin lesion
    - Fomites
  - Diagnosis:
    - Gram stain and culture
    - PCR
    - Diphtheria antibodies
    - Elek's test for toxin

- Treatment:
  - First choice: diphtheria antitoxin + erythromycin or penicillin
  - Second choice: diphtheria antitoxin + azithromycin and clindamycin
  - Immunization

2.3.3.2 Corynebacterium urealyticum

- Corynebacterium urealyticum is a slow-growing, urease-positive, multidrug-resistance Gram-positive bacteria
- **Virulence factors:**
  - Adhesive pili: colonization and adherence to host tissue; bacteria colonize the human skin and urinary tract and have a predilection for uroepithelial cells
  - Hydrophobicity: promotes the bacteria to form biofilms on medical devices
  - Urease activity: converts urea to ammonia, which results in alkalization of urine and formation of struvite stone
- **Clinical significance:**
  - Opportunistic nosocomial pathogens
  - Responsible for uncommon cause of UTI and bladder stones
- **Choice of antibiotics:**
  - Frist choice: vancomycin, linezolid, and daptomycin
  - Second choice: telecoplanon, ciprofloxacin, and levofloxacin

2.3.3.3 Rhodococcus equi (R. equi)

- Formerly known as *C. equi* is a soil bacteria present in the guts of many herbivores and spreads via animal dung, manures, and farm area
- *R. equi* is a facultative intracellular bacteria that infect macrophages, where it survives and grows
- Rare cause of subacute cavitary lung infections; mimics tuberculosis in immunocompromised patients
- Responsible for rare cases of brain and skin abscess
- Antibiotics:
  - First choice: vancomycin or imipenem + levofloxacin + rifampin or azithromycin
  - Second choice: linezolid + fluoroquinolone or aminoglycoside + rifampin

2.3.3.4 Other Corynebacterium

- Involved in rare cases of prosthetic valve endocarditis, UTI, prostatitis, and other prosthetic devices; however, they are not a very common cause of infections

2.3.3.5 Listeria monocytogenes

- Gram-positive, facultative intracellular, motile, with characteristic tumbling motility under light microscopy, bacilli
- Habitat of soil, decaying vegetables, animal feed, water, sewage, and human food

- **Virulence factors:**
  - Spread cell to cell without exposure to the extracellular space
  - Listeria can survive and reproduce in low temperatures (34–40°F)
  - Secret listeriolysin O, which is a pore-forming toxin; it suppresses T-cell activation
  - Internalins: bacterial surface proteins, which help the bacteria in attaching to host cells
  - Phosphatidylinositol-specific phospholipase helps the bacteria to escape from the host cell's vacuole
- **Clinical significance:**
  - Responsible for meningitis, bacteremia, encephalitis, gastroenteritis, and endocarditis
  - Most common cause of bacterial meningitis in patients with underlying neoplastic disease, organ transplant, and immune-compromised patients
  - Infection in pregnancy may result in fetal loss, premature birth, or infected newborn (neonatal sepsis, meningitis, and death)
- **High risk group:**
  - ➢ Neonates
  - ➢ Older people >60 of years age
  - ➢ Pregnant women
- Mostly transmitted through food
- High-risk contaminated food with Listeria are
  - ➢ Raw unpasteurized milk and anything made of it
  - ➢ Undercooked hot dogs, meat, deli meat, and poultry
  - ➢ Refrigerated smoked seafood
  - ➢ Unwashed salad, raw fruits, and vegetables, including sprouts
- First-choice antibiotics:
  - Ampicillin ± gentamicin for meningitis and encephalitis
  - Bacteremia → ampicillin
- Second-choice antibiotics
  - Trimethoprim-sulfamethoxazole
  - Meropenem

2.3.3.6 Nocardia

- Gram-positive, branching filamentous rod-shaped, obligate aerobic bacteria Nocardia is catalase positive and has superoxide dismutase. Catalase turns hydrogen peroxide into water and superoxide dismutase and breaks the superoxide radicals into oxygen and hydrogen peroxide.

www.images.google.com
to see the images of pulmonary and cutaneous nocardiosis.

- There are several species that cause disease in humans
- Present worldwide and founds in standing water, decaying plants, and soil
- Mostly infect immunocompromised and elderly patients
- Responsible for nocardiosis, which is divided into three forms
  a) Pulmonary
  b) Disseminated
  c) Cutaneous
  a) Pulmonary nocardiosis: nonspecific symptoms like cough, fever, chill, chest pain, anorexia, and weight loss; this could progress to suppurative pneumonia, cavitary pulmonary lesions, and pleural effusion
  b) Disseminated nocardiosis: usually is a complication of pulmonary nocardiosis and spreads to the central nervous system or heart, where it causes brain abscess, meningitis, or endocarditis
  c) Cutaneous nocardiosis: bacteria causes a local infection like cellulitis, characterized by pus filled blister, ulcer, lymphocutaneous syndrome, or actinomycetoma (suppurative nodules with drainage fistula); mimics sporotrichosis
- Diagnosis:
  ➢ Smear or culture
  ➢ Radiograph
  ➢ Brain MRI
- Treatment:
  ➢ Mortality is >50% even after the treatment
  ➢ First choice:

  Trimethoprim-sulfamethoxazole + imipenem-cilastatin for PNA and brain abscess
  TMP-SMX for skin infection

  ➢ Second choice

  Linezolid + meropenem
  Tetracycline for skin lesions

2.3.3.7 Anaerobic Gram-positive bacilli see Chapter 3, Section 3.3

2.4 Summary of gram positive bacteria

See Table 2.2.

Table 2.2 Gram-positive bacteria and treatment options.

Pathogen	Disease	Antibiotics	
		First choice	**Second choice**
Gram-positive cocci			
Staph. aureus	Bacteremia Endocarditis Osteomyelitis Pneumonia Skin infection Septic arthritis	Nafcillin or oxacillin, cefazolin, dicloxacillin, cephalexin MRSA: vancomycin, linezolid, daptomycin	Clindamycin, TMP-SMX, levofloxacin, doxycycline Carbapenem MRSA: clindamycin, tetracycline, tigecycline VISA and VRSA: daptomycin Ceftaroline, linezolid, tigecycline, chloramphenicol
Staph. epidermidis	Prosthetic device infection, catheter-associated infection, prosthetic valve endocarditis	Nafcillin or oxacillin, cefazolin, dicloxacillin, cephalexin, vancomycin, linezolid, daptomycin	Clindamycin, TMP-SMX, levofloxacin, doxycycline, carbapenem, tetracycline, tigecycline
Staph. saprophyticus	Urinary tract infection	TMP-SMX, cefazolin, cephalexin, cefaclor	Clindamycin, amox-clav, levofloxacin, chloramphenicol, doxycycline, tetracycline, vancomycin, daptomycin, nitrofurantoin
S. pyogenes	Strep throat, dental infection, skin infection, scarlet fever, strep throat, strep toxic shock syndrome	Penicillin VK, penicillin G, amoxicillin, cephalexin	Azithromycin, clindamycin, vancomycin, linezolid, carbapenem, cephalosporin
S. agalactiae	Meningitis, sepsis, PNA in neonates, endometritis, bacteremia, spontaneous abortion, UTI, septic arthritis in postpartum women	Penicillin G or VK, ampicillin, cefazolin	Vancomycin, ceftriaxone, clindamycin, cephalosporin, carbapenem
Viridans group	Dental infection, subacute endocarditis, abscess in various organs	Ceftizoxime, ceftriaxone, vancomycin, penicillin, ampicillin	Clindamycin, cephalosporin, linezolid
S. pneumoniae	Pneumonia, otitis media, meningitis, septic arthritis, endocarditis	Penicillin G or VK, ceftriaxone, levofloxacin, vancomycin	Cefepime, IV cephalosporins, linezolid, doxycycline, moxifloxacin, clindamycin, amoxicillin-clavulanate
Enterococcus	Hospital acquired UTI, wounds infection, prosthetic valve endocarditis, IV catheter infection	Ampicillin, vancomycin, penicillin G, nitrofurantoin for cystitis See Section 2.2.2.4.1	Daptomycin, ± ceftriaxone, ceftaroline, linezolid
Gram-positive bacilli			
Spore forming			
B. anthracis	Cutaneous anthrax, pulmonary anthrax, GI anthrax	Amoxicillin or penicillin VK, ciprofloxacin	Clindamycin, doxycycline, levofloxacin
B. cereus	Watery diarrhea	Enterotoxin, no antibiotics needed. Vancomycin for bacteremia, clindamycin	Fluoroquinolone, imipenem, aminoglycoside

Table 2.2 Gram-positive bacteria and treatment options.—cont'd

Pathogen	Disease	Antibiotics	
		First choice	**Second choice**
Nonspore forming			
Corynebacterium diphtheriae	Respiratory tract infection, myocarditis, neuritis	Diphtheria antitoxin + erythromycin or penicillin	Azithromycin, clindamycin
Corynebacterium urealyticum	Urinary tract infection	Vancomycin, linezolid, daptomycin	Telecoplanon, ciprofloxacin, levofloxacin
Listeria monocytogenes	Meningitis, bacteremia, encephalitis, endocarditis	Ampicillin ± gentamycin	TMP-SMX, meropenem, linezolid, levofloxacin, piperacillin-tazobactam
Nocardia	Nocardiosis	TMP-SMX + imipenem-cilastatin, TMP-SMX for skin abscess	Linezolid + meropenem, imipenem-cilastatin + amikacin, tetracycline for skin infection

Amox-clav, amoxicillin-clavulanate; *Pen*, penicillin G; *TMP-SMZ*, trimethoprim-sulfamethoxazole.

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3 Anaerobic bacteria

Signs of anaerobic infection:

- Suppurative infection
- Infection with gas formation
- Tissue necrosis with foul smell
- Positive gram stain but negative aerobic culture

3.1 Classification

a) Gram-positive anaerobic cocci
b) Gram-positive anaerobic bacilli
c) Gram-negative anaerobic cocci
d) Gram-negative anaerobic bacilli

3.2 Gram-positive anaerobic cocci

- Includes: *Peptococcus*, *Peptostreptococcus*, *Micromonas* + 15 more
- Part of the normal flora of upper respiratory tract, GI tract, and vagina
- Mostly cause local dental infection and endometritis
- Rarely associated with endocarditis, bacteremia, and brain abscess
- Antibiotics of first choice:
  - Penicillin and amoxicillin
- Second choice:
  - Metronidazole
  - Clindamycin

3.3 Gram-positive anaerobic bacilli

Classified into:

1) Spore forming
  - *Clostridium botulinum*
  - *Clostridium tetani*
  - *Clostridium perfringens*
  - *Clostridium difficile*

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2) Nonsporing
- Lactobacillus
- Actinomyces
- Propionibacterium

3.3.1 Spore-forming gram-positive anaerobic bacilli

3.3.1.1 Clostridium botulinum

- Gram-positive bacilli, obligate anaerobic, spore-forming bacteria.
- Can be isolated from deep compact soil, fruit, vegetables, seafood, and processed foods.
- Spores or bacteria can contaminate the food, infect wounds, or enter the respiratory tract by inhalation. Spores germinate and become mature bacteria and secrete toxins.
- Spores are highly heat resistant and can survive for many hours at 100°C. Moist heat at a temperature of 120°C for 30 min can destroy the spores.
- Virulence factors:
  - Production of toxins is the main pathogenesis of the bacteria and is the most lethal substance known so far.
  - Eight distinct (A–H) types of toxins have been isolated, which varies in toxicity. Toxins C and D cause disease in the animal, while the rest of the strains infect human.
  - Bacteria release neurotoxin that is taken up by neurons.
  - Toxin cleaves SNARE proteins in neuronal cells, which is necessary for the release of acetylcholine.
  - Inhibiting the release of acetylcholine at the peripheral nerve endings and causes flaccid, descending paralysis, including cranial nerve palsy.
- Clinical relevance:
  - Responsible for botulism.

3.3.1.1.1 Botulism

- Classified into:
  - Foodborne botulism: Mostly result from preformed neurotoxin. Canned foods are the major source of infection. Symptoms start 18–36 h after ingestion of food contaminated with toxins and range from mild to fatal within 24 h.
  - Wound botulism: Wounds are infected with *C. botulinum* spores or bacteria itself. The spore germinates in an anaerobic environment and produces neurotoxins. Intravenous (IV) drug user, especially black tar (heroin) injection has been associated with botulism.
  - Inhalation botulism: Spores are inhaled where they germinate and secret toxins.
  - Infant botulism: Usually infect children less than one year old due to incomplete normal gut flora permit the growth of the harmful bacteria. Most common source is the ingestion of contaminated soil or dust. Ingestion of raw honey has also been associated with infant botulism.

  - Bioterror botulism: Botulinum toxin has been identified as a potential agent for bioterrorism.
  - Iatrogenic botulism: Cases of botulism have been reported in patients who received botulism toxin for cosmetic purpose.
- Sign and symptoms:
  - Dryness of mouth, blurred vision, slurred speech, symmetrical bilateral cranial nerve palsy, muscles weakness followed by descending paralysis, dyspnea, shortness of breath, and respiratory failure.
  - Affected person is usually afebrile, normal blood pressure, and normal or slow heart rate.
  - Sensory nerves are not affected except blurred vision.
  - Hypothermia, urinary retention, dry mouth, posterior hypotension, and constipation due to autonomic system dysfunction.
  - Death results from paralyses of respiratory muscles (diaphragm).
  - Infant botulism is characterized by constipation in most of the cases.
  - Foodborne botulism: Nausea, vomiting, abdominal pain, and diarrhea usually start earlier before the start of typical botulism symptoms of neuropathies and descending flaccid paralysis.
  - Wounds botulism present with neurological finding in the absence of gastrointestinal symptoms.
  - Inhale botulism has the same symptoms as gastrointestinal botulism.
- Risk factors:
  - Contaminated food
  - Young children/infants
  - Ingestion of raw honey
  - IV drug user (Fig: www.images.google.com)
  - Crush injury
  - Exposure to reptile
- Diagnosis:
  - Clinical
  - Toxin assay
  - Polymerase chain reaction (PCR)
- Differential diagnosis:
  - Guillain–Barre syndrome
  - Amyotrophic lateral sclerosis
  - Myasthenia gravis
  - Stroke
  - Tick paralysis
  - Shellfish poisoning
- Treatment:
  - Supportive

- Heptavalent botulinum antitoxin → only bind to free toxin and do not reverse the toxin effects that are already bound to the receptors. Used for children older than one-year-old and adults.
- Human botulinum immune globulin → used for infant less than one-year-old.
- Antibiotics are usually not used for infant and adult gastrointestinal botulism. However, antibiotics can be used for wound botulism. Penicillin or metronidazole is used but have unproven result in clinical trials.
- Tetracycline, aminoglycoside, and polymyxins should be avoided because these antibiotics potentiate the effects of toxin by inducing neuromuscular blockade.
- Botulinum toxin is also used medically for the treatment of hyperhidrosis, achalasia, focal dystonia, and removing wrinkles (cosmetology).

3.3.1.2 Clostridium tetani

- Gram-positive obligate anaerobe, spore-forming bacilli.
- Isolated from deep, compact soil and the gut of mammals. They love to live in oxygen-free environment.
- Virulence factors:
  - Secretion of toxin.
  - Toxin produced by the bacteria is called tetanospasmin (neurotoxin). The toxin is taken by a motor neuron (inhibitory neurons called Renshaw cells). Inside the cell, it cleaves the SNARE proteins that are necessary for the release of inhibitory neurotransmitters like glycine and GABA. Inhibiting the release of inhibitory neurotransmitters results in the unopposed firing of the excitatory neurotransmitter acetylcholine.
  - Unopposed action of acetylcholine results in skeleton muscle spasms (tetany).
  - Incubation period ranges from 3 to 21 days.
- Clinical relevance:
  - Responsible for tetanus.

3.3.1.2.1 Tetanus

- Generalized tetanus: Most common form and involves all body.
- Local tetanus: Affects localized area such as contraction one extremity, or just board like abdomen.
- Cephalic tetanus: Involves some head injuries and infects cranial nerves.
- Neonatal tetanus: Unhygienic cutting of the umbilical cord; chances are increased if the mother is not immunized. The infant is unable to open the mouth due to facial muscle spasms. Rigid and opisthotonos body, increased muscle tone, clenched hands, and feet dorsiflexed.

www.images.google.com

- Signs and symptoms:
- Characterized by powerful, violent muscle spasms
- Lockjaw or jaw stiffness → trismus
- Facial spasm produces a specific smiley face called risus sardonicus
- Dysphagia
- Tonic muscle spasms
- ↑sympathetic activity causes excessive sweating, difficulty in swallowing, and the problem with urination
- Board like rigid abdomen
- Symptoms last for four to six weeks or until the generation of a new axonal nerve
- High mortality rate (respiratory failure)

• Risk factors:
  - Unimmunized
  - Injury (specially uncleaned wound)
  - Aseptic obstetric or other surgery
  - Unhygienic IV drug user
  - Patients with dental infection
  - Diabetic patients with infected extremity ulcers
• Diagnosis
  - Clinical and history
  - Serum and urine sample for toxin assay
  - Spatula test → absence gag reflex
  - Culture is very difficult
• Differential diagnosis:
  - Meningitis/encephalitis
  - Seizure
  - Dystonia
  - Strychnine poisoning
• Treatments:
  - Secure airways
  - Wound debridement
  - Tetanus antitoxin → limited effect, as it only binds to the unbound toxins. Toxins that already bind nerve terminals cannot be reversed
  - Antibiotics:
    - First choice: Metronidazole or penicillin
    - Second choice: Doxycycline
  - Muscles relaxants or benzodiazepines for muscles spasms
  - Prevention: Vaccine is available as TDap for children and Td for adults

3.3.1.3 *Clostridium perfringens*

- *C. perfringens* is gram-positive, nonmotile, pleomorphic anaerobic bacilli. It is isolated in nature, mostly in uncooked poultry or meat, and decaying vegetables.
- Virulence factors:
  - *C. perfringens* produces several toxins such as alpha, beta, epsilon, and iota. These toxins damage the tissue, blood vessels, and blood cells.
  - Bacteria also produce toxin hemolysin, which is involved in tissue damage.
  - Enterotoxin is responsible for food poisoning.
  - *C. perfringens* produces histotoxic gas through glucose fermentation, which is a characteristic sign.
- Clinical relevance:
  - Necrotizing fasciitis
  - Muscles gangrene (gas gangrene)
  - Toxic shock syndrome
  - Clostridial necrotizing enteritis
  - Biliary infection
  - Food poisoning → diarrhea and abdominal cramp. Top five most common etiology for foodborne disease outbreaks.
- Risk factors:
  - Food high in protein and starch is produced in large quantities and kept warm for a long time before serving, such as in prisons, schools, hospitals, long-term care facilities, and catering food. This gives the bacteria time to grow.
  - Raw meat, poultry, dried and precooked food.
  - Elderly, children, and patients with the weak immune systems are at high risk to get sick.
- Diagnosis:
  - Clinical
  - Gram stain and culture
  - Enterotoxin in stool for food poisoning and necrotizing enteritis.
- Differential diagnosis:
  - Viral infectious diarrhea
  - Other bacterial infectious diarrhea
  - Appendicitis
  - Ischemic colitis
  - *Staphylococcus aureus* infection
  - *Streptococcus pyogenes* infection
- Treatments:
  - Surgical debridement and drainage (see Table 3.1)
  - Penicillin G with clindamycin
  - Metronidazole ± clindamycin

- Doxycycline
- Supportive treatment for acute gastroenteritis

Table 3.1 Prophylaxis wound management.

	Clean wound		Dirty wound	
History	**Td**	**TIG**	**Td**	**TIG**
Unknown vaccine history or partially vaccinated	Yes	No	Yes	Yes
Fully vaccinated	Yes if > 10 yrs	No	Yes if > 5 yrs	No

Td = tetanus diphtheria vaccine; TIG = tetanus immune globulin.

For children <7 years old, use TDap or TD.

3.3.1.4 Clostridium difficile

- Gram-negative anaerobic, spore-forming, drumstick-shaped bacteria.
- Transmitted by fecal oral route.
- About 3%–7% of healthy adults are asymptomatic carriers and carry the bacteria in their large intestines.
- Risk factors:
  - Usually associated with the use of antibiotics, but other risk factors also exist, such as:
  - Hospital stay longer than a week
  - Nursing home patients
  - Underlying disease
  - Extreme ages group
  - Use of proton inhibitors and H_2 blockers
- Virulence factors:
  - Produce two potent enterotoxins:
    - Toxin A
    - Toxin B
  - Toxin A destroys the cytoskeleton of intestinal cells and activate neutrophils and other inflammatory mediators, which result in mucosal injury and tight junctions between cells falling apart.
  - Toxin B is more potent than toxin A and is a cytotoxin. Both toxins work together and are responsible for pseudomembrane colitis and diarrhea.
  - Hypervirulent strain NAP1/BI/027 has been isolated in some ICU patients, which causes severe disease and is difficult to treat.
- Clinical relevance:
  - Watery diarrhea ± blood
  - May result in toxic megacolon, especially if antimotility drugs are used

  - Abdominal cramping
  - No nausea and vomiting
  - Fever
  - Weakness
- Complications:
  - Pseudomembranous colitis
  - Toxic megacolon
  - Colonic perforation
  - Septicemia
  - Kidney failure
- Diagnosis:
  - Clinical
  - Stool assay for *C. difficile* antigen (glutamate dehydrogenase) and toxin.
  - PCR test for *C. difficile's* toxin gene.
  - Sigmoidoscopy for pseudomembrane.
  - CT or abdominal X-ray for any perforation or megacolon.
- Differential diagnosis:
  - Crohn's disease
  - Ulcerative colitis
  - Diverticulitis
  - Irritable bowel syndrome
  - Malabsorption
  - Infectious diarrhea (viral/other bacterial).
- Treatment:
  - Oral vancomycin or fidaxomicin
  - Nitazoxanide (not used in the United States of America)
  - For recurrence → repeat the antibiotics and add rifaximin. Still refractory, use fecal transplant.
  - Monoclonal antibody, bezlotoxumab neutralizes the toxin.
  - Surgery is the last resort.

3.3.2 Nonsporing gram-positive anaerobic bacilli

3.3.2.1 Actinomyces

- Gram-positive, anaerobic, nonspore-forming bacteria with guanine-cytosine content.
- Filamentous bacteria resemble to fungi.
- Actinomyces has several species; *Actinomyces israelii* is the most common species involved in human infection.
- Actinomyces is a part of normal flora of gums, teeth, tonsils, intestine, and vagina.
- Causes granulomatous and suppurative infection in immune-compromised patients.

- Virulence factors:
  - Adhesins
  - Bacteriocin
  - Invasins
  - Antibiotic resistance
- Clinical relevance:
  - Responsible for actinomycosis

3.3.2.1.1 Actinomycosis

- Signs and symptoms
  - Depending on the site of infection
  - Most common form is cervicofacial actinomycosis (lumpy jaw syndrome): Local injury, surgery, or trauma progress to abscess and result in growth of the bacteria, which forms sinus track and drains purulent yellowish discharge containing granules that look like sulfur skin. Severe cases may result in complications such as osteomyelitis, otitis media, or infection reaches to brain.
  - Lung form causes pneumonitis that resembles to tuberculosis with symptoms of productive cough with pus or blood, fever, and chest pain.
  - Abdomen form involves the intestine and is associated with pain, fever, vomiting, diarrhea, or constipation and may result in partial obstruction of the intestine.
  - Rarely may cause pelvic inflammatory disease in females who have intrauterine devices for long periods.
- Risk factors:
  - Diabetics
  - Alcoholism
  - Poor dental hygiene
  - Immunosuppression
  - Malnutrition
  - Surgery
- Complications:
  - Bacteremia
  - Osteomyelitis
  - Pneumonia
  - Pericarditis
  - CNS infection
- Diagnosis:
  - Gram stain and microscopic exam
  - Culture → takes 21 days or more to grow
- Differential diagnosis:
  - Aspiration pneumonia
  - Tuberculosis

  - Nocardiosis
  - Lung abscess
  - Dental abscess
- Treatment:
  - First choice: Long-term high-dose penicillin, ampicillin
  - Second choice: doxycycline or clindamycin
  - Piperacillin-tazobactam
  - Ceftriaxone
  - Removal of IUD in PID actinomycosis
  - Surgery and drainage

3.3.2.2 Lactobacillus sp.

- Microaerophilic
- Part of normal flora of intestine and genitourinary tract
- Cause urinary and digestive tract infection in immunocompromised patients
- Also involve in small intestine bacterial overgrowth syndrome (Streptococci, Bacteroides, *E. coli*, Lactobacillus, and Klebsiella)
- Diagnosis:
  - Urinalysis
  - Microscopic exam
  - Culture
  - PCR
- Treatment:
  - Penicillin
  - Ampicillin
  - Clindamycin

3.3.2.3 Propionibacterium

- Several species, mostly nonpathogenic and are part of normal flora of skin, sebaceous glands, and hair follicles.
- *Propionibacterium acne* is the most common cause of acne vulgaris.
- *Propionibacterium freudenreichii* is used in Swiss cheese manufacturing.
- Rarely involves in brain abscess, dental infection, endocarditis, prosthetic joint infection, and osteomyelitis.
- Third most common cause of cerebrospinal fluid shunt infection.
- Also involve in breast implant infection.
- Diagnosis:
  - Clinical
  - Culture
  - PCR

- Treatment:
  - Topical antibiotics such as doxycycline and erythromycin for mild to moderate acne
  - Oral antibiotics such as doxycycline, minocycline, and erythromycin for moderate to severe acne
  - For systemic infection:
    - First choice
      - ➢Penicillin G
      - ➢Ceftriaxone
    - Second choice:
      - ➢Vancomycin
      - ➢Daptomycin
      - ➢Linezolid

3.3.3 Gram-negative anaerobic cocci

3.3.3.1 Veillonella species

- Part of normal flora in the oropharynx, gastrointestinal tract, and female genital track. Rarely cause infections such as meningitis and endocarditis.
- Antibiotics:
- First choice: Metronidazole, piperacillin-tazobactam.
- Second choice: Meropenem, amoxicillin-clavulanate.

3.3.4 Gram-negative anaerobic bacilli

3.3.4.1 Bacteroides

- Gram negative, rod-shaped, nonspore-forming, obligate anaerobic bacteria.
- More than 30 species have been recognized. *Bacteroides fragilis* is the most common and virulent Bacteroides.
- Most common anaerobic bacteria of gut flora where they have mostly symbiotic relationship with the host. Bacteria assist in the breakdown of complex food molecules and release nutrients for the body use.
- Virulence factors:
  - Lipopolysaccharide capsule: Escapes phagocytosing the bacteria by immune cells.
  - Generate succinic acid: Inhibits neutrophils to neutralize the bacteria.
  - Enterotoxigenic: Secretes heat-labile zinc metalloprotease toxin that stimulates IL-8 and other cytokines that destroy intestinal cells and cause inflammatory diarrhea.
  - Bacteria are a part of the normal flora of the gut. However, responsible for many infections once outside the gut.
  - Bacteria are resistant to many antibiotics, including broad-spectrum antibiotics.

- Clinical relevance:
  - Appendicitis
  - Peritonitis
  - Abdominal abscess
  - Diabetic foot ulcer
  - Pneumonia and lung abscess
  - Brain abscess
  - Cellulitis
  - Dental infection
- Risk factors:
  - Recent surgery
  - Trauma
  - Malignancy
  - Diabetics
  - Immunocompromised
- Diagnosis:
  - Anaerobic culture
  - PCR
- Treatment:
  - First choice: Metronidazole
  - Second choice: Piperacillin-tazobactam, meropenem, amoxicillin-clavulanate
- Other bacteria: Uncommon and rarely cause infection. These include the following:

3.3.4.2 Fusobacterium

- Gram-negative, obligate anaerobic, nonspore-forming bacterium. Bacterium is rod-shaped with pointed ends. Previously it was believed that the bacterium was a part of normal flora of the mouth, but recent studies have shown that the presence of fusobacterium in mouth is pathogenic.
- Associated with wound infections, abscess, lung, intracranial infections, and Lemierre syndrome.
- Lemierre syndrome is a rare complication of oropharyngeal infection which results in the extensions of the infection to lateral pharyngeal space of the neck with subsequent septic thrombophlebitis of internal jugular vein, septicemia, and death.

3.3.4.3 Porphyromonas

- Gram-negative, obligate anaerobic, nonspore-forming bacteria belong to a family Porphyromonadaceae.
- Cause aspiration pneumonia and dental infection.

3.3.4.4 Prevotella

- Gram-negative, obligate anaerobic, nonspore-forming bacteria. Part of normal flora of gut, vagina, and mouth.
- Responsible for intraabdominal and soft tissue infection.

3.3.4.4.1 Treatment

- Antibiotics:
- First choice: Metronidazole
- Second choice: Piperacillin-tazobactam, meropenem, amoxicillin-clavulanate.

3.4 Summary of anaerobic bacteria and selection of antibiotics

See Table 3.2.

Table 3.2 Anaerobic bacteria and treatment options.

Anaerobic bacteria			
		1st choice	**2nd choice**
Gram-positive anaerobic cocci			
Peptococcus, Peptostreptococcus, +15 more	Dental infection, endometritis, bacteremia, brain abscess	Penicillin, amoxicillin, ampicillin	Clindamycin, doxycycline ± metronidazole, vancomycin, daptomycin
Gram-positive anaerobic bacilli			
Spore forming			
Clostridium botulinum	Botulism	Supportive, antitoxin, human botulinum immune globulin, penicillin, metronidazole	None
Clostridium tetani	Tetanus	Wounds debridement, antitoxin, metronidazole, penicillin G	Doxycycline
Clostridium perfringens	Necrotizing fasciitis, gas gangrene. Toxic Shock Syndrome, necrotizing enteritis, biliary infection	Penicillin G ± clindamycin, surgical debridement, and drainage	Doxycycline, erythromycin, chloramphenicol, cefazolin, ceftriaxone, metronidazole
Clostridium difficile	Watery diarrhea ± blood, pseudomembrane colitis	PO vancomycin, fidaxomicin	None
Non–spore forming			
Lactobacillus	Normal flora of intestine, bacterial overgrowth syndrome, malabsorption. Infection in immunocompromised patients	Penicillin G, ampicillin	Clindamycin
Actinomyces	Actinomycosis	Ampicillin, penicillin G, amoxicillin, erythromycin	Doxycycline, clindamycin, ceftriaxone
Propionibacterium	Acne infection, infect orthopedic devices, prosthetic heart valve	Penicillin G, ceftriaxone	Doxycycline, vancomycin, daptomycin

Continued

Table 3.2 Anaerobic bacteria and treatment options.—cont'd

Anaerobic bacteria			
		1st choice	**2nd choice**
Gram-negative anaerobic cocci			
Veillonella sp.	Rarely cause infection such as meningitis or endocarditis	Metronidazole	Meropenem, amoxicillin-clavulanate. Piperacillin-tazobactam
Gram-negative anaerobic bacilli			
Bacteroides	Intraabdominal infection	Metronidazole, piperacillin-tazobactam	Meropenem, ertapenem, amoxicillin-clavulanate
Fusobacterium	Wound infection, abscess in lungs	Same as above	Same as above
Porphyromonas	Pneumonia, dental infection	Same as above	Same as above
Prevotella	Soft tissue infection	Same as above	Same as above

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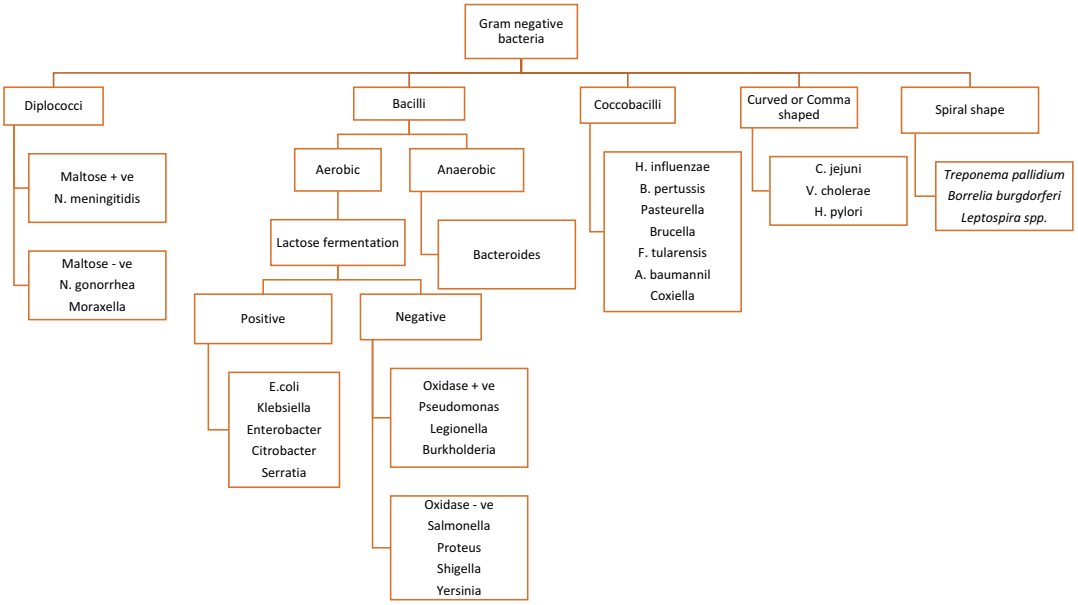
4 Gram-negative bacteria

4.1 Classification



4.2 Gram-negative cocci

- *Neisseria meningitides*
- *Neisseria gonorrhoeae*
- Moraxella
- Kingella species (coccobacilli)

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4.2.1 *Neisseria meningitidis*

- Gram-negative diplococci, obligate aerobic bacteria, nonspore forming, and nonmotile
- Catalase and oxidase positive, and grows on Thayer–Martin agar
- It ferments maltose which differentiates it from *Neisseria gonorrhea*
- Causes meningitis, sepsis, and septic shock in infants, children, and young adults
- About 5% of people are asymptomatic carriers, harvesting the bacteria in the nasopharynx area
- Virulent factors:
  - Capsule: Made up of polysaccharide and having a highly charged outer layer prevents the bacteria from being phagocytized by the host immune cells
  - Pili: Help the bacteria for attachment with host cells
  - Opacity protein: Express two proteins, Opa and Opc, from the outer membrane. These proteins help the bacteria to attach to the host cells
  - Toxins: IgA protease that destroys immunoglobulin A. IgA plays an important role in protecting the host from invading bacteria
  - Produce factor H-binding protein: Deactivate factor H that plays an important role in complement pathway as antibacterial
  - Produce catalase that breaks hydrogen peroxide molecule inside the neutrophils. This helps the bacteria to survive and take over neutrophils and multiple inside the cell
  - Produce several other toxins that destroy cells of capillaries and damage endothelial cells, which release procoagulant-like factors, and other inflammatory mediators, resulting in disseminated intravascular coagulation (DIC)
- Risk factors
  - Children aged 6 months to 3 years
  - Adolescents, college freshmen living in a dormitory
  - Military recruits
  - Asplenic patients or patients with complement deficiency
  - AIDS patients
- Clinical relevance:
  - Meningitis
  - Meningococcemia
  - Pneumonia
  - Septic arthritis
  - Pericarditis
  - Sepsis
  - Signs and symptoms:
    - Typical meningitis signs such as fever, headache, stiff neck, photophobia, nausea, and vomiting. + Kernig and Brudzinski sign

    - Classical petechial rash (nonblanching) appears soon after the onset of disease
    - Meningococcemia causes multiorgan failure, DIC, Waterhouse–Friderichsen syndrome (adrenal hemorrhage → profound shock)
    - High mortality rate
- Diagnosis:
    - Lumbar puncture and cerebrospinal fluid (CSF) analysis
    - Gram stain and culture → Thayer–Martin agar
    - Polymerase chain reaction (PCR)
    - Serological tests
- Differential diagnosis:
    - Bacterial meningitis other than *Neisseria meningitidis*
    - Viral/fungal meningitis
    - Pharyngitis
    - Intracranial hemorrhage
    - Headache
- Treatment:
    - First choice: Third-generation cephalosporin → ceftriaxone + dexamethasone
    - Penicillin G IV and ampicillin IV
    - Second choice → ciprofloxacin or levofloxacin, (efficacy is not well established), chloramphenicol, meropenem, aztreonam
- Prophylaxis:
    - Rifampin for children → 5–10 mg/kg q 12h for four doses
    - Ceftriaxone 250 mg × 1
    - Ciprofloxacin or levofloxacin 500 mg × 1 dose
    - Vaccine → meningococcal vaccine is available for high-risk patients

4.2.2 *Neisseria gonorrhea* Please also see Chapter 10 for more information

- Diplococci, aerobic, intracellular bacteria
- Catalase and oxidase positive and maltase negative
- Cause gonorrhea which is a sexually transmitted disease
- Infect urethra, cervix, rectum, pharynx, and conjunctiva. Disseminated disease affects the skin, joints, heart, and perihepatic site
- Virulence factors:
    - Type IV pili: Play an important role in attaching to human mucosal epithelial cells, fallopian tube, and vaginal epithelial cells. Pili also help the bacteria for motility.

  - Por protein: Plays a role in the transport of ions and nutrients across the outer membrane.
  - Opa protein: Specific binding protein.
  - Lipooligosaccharide (LOS): Triggers widespread immune reaction and sepsis.
  - IgA protease: Cleaves IgA and LAMP1 which lead to bacterial survival.
- Clinical relevance:
  - Sign and symptoms:
  - Depends on the site of the infection
  - Male urethritis → penile tenderness, dysuria, and purulent discharge
  - Cervicitis → inflammation and easily bleed cervices with purulent discharge, dysuria, and vulvar irritation are common
  - Fitz-Hugh-Curtis syndrome → perihepatic adhesions, inflammation of liver capsule, and complications of pelvic inflammatory disease (PID) result in right upper quadrant pain, fever, nausea, and vomiting. Mostly in women
  - Conjunctivitis in newborn
  - Most common causes of PID are gonorrhea and chlamydia
  - Responsible for polyarthritis, septic arthritis, skin lesions, fever, epididymitis, and prostatitis that are several other manifestations of gonorrhea
  - Gonococcal septic arthritis infects large joints and sometimes with skin lesions
- Diagnosis
  - Gram stain and culture
  - Nucleic acid amplification tests (NAATs)
  - Screening → urine sample should be screened by NAAT for high-risk patients
- Choice of antibiotic
  - First choice: Ceftriaxone + azithromycin or doxycycline
  - Second choice: Spectinomycin + azithromycin, gentamicin + azithromycin
  - No vaccine is available

4.2.3 *Moraxella catarrhalis*

  - Gram-negative diplococci morphologically resemble Neisseria
  - Does not grow in Thayer–Martin agar
  - Colonizes upper respiratory tract in 40%–50% of normal school children
  - Causes otitis media in young children (third most common cause) and second most common cause after *Haemophilus influenza in* exacerbates COPD in smokers. It is also responsible for pneumonia in elderly patients
  - Many strains produce B-lactamase
- Choice of antibiotic:
  - First choice: Amoxicillin-clavulanate or cefuroxime
  - Second choice: Azithromycin, TMP-SMX, cefprozil, or cefdinir

4.2.4 Kingella species

- Belong to a family Neisseriaceae, coccobacilli, oxidase positive, non-motile bacteria that appears in pairs or short chains. Closely resemble to Neisseria species.
- Part of HACEK group
- Colonize upper respiratory tract
- Cause osteomyelitis, endocarditis, bacteremia, and septic arthritis
- Rarely cause pneumonia, meningitis, and ocular infection
- Choice of antibiotics:
  - First choice: Penicillin G or cephalosporin IV
  - Second choice: TMP-SMX, erythromycin or tetracycline, or fluoroquinolone

H=Haemophilus sp.
A=Aggregatibacter sp.
C=*Cardiobacterium hominis*
E=*Eikenella corrodens*
K=Kingella sp.
Group together cause 5%−10% cases of community acquired native valve endocarditis

4.3 Gram-negative bacilli

This is a very large group and include bacilli, coccobacilli, curved or comma shaped gram negative bacteria. Clinically, this group can also be divided according to the site of infection, site of colonization, or source of infections

a) Enterics
b) Zoonotic
c) Hospital acquired
d) Respiratory

4.3.1 Enterics

These pathogens are part of the intestinal flora of humans or animals. Most of them cause gastrointestinal disease and are acquired by fecal oral route or unsanitary conditions

The group includes:

1) Enterobacteriaceae
2) Vibrionaceae
3) Bacteroidaceae (anaerobic) → See Chapter 3, Section 3.3.4.1.

4.3.1.1 Enterobacteriaceae

Large family. Can be divided into (Table 4.1):

Table 4.1 Classification of Enterobacteriaceae.

Lactose fermenting	Nonlactose fermenting
Escherichia coli	*Proteus mirabilis*
Klebsiella pneumoniae	*Shigella dysenteriae*
Serreta	*Salmonella typhi* and nontyphi group
Enterobacter	*Yersinia enterocolitica*

4.3.1.1.1 Lactose fermenting

Most are part of the normal flora of human intestine.

4.3.1.1.1.1 Escherichia coli

- Most abundant gram-negative bacteria in the large intestine and part of normal flora
- Catalase positive, lactose fermenter, indole positive, capsulated bacteria with flagella
- Various serotypes,
- Transmission is usually via fecal oral route, contaminated water, undercook hamburger or meat, and unpasteurized milk
- Virulence factors:
  - Adhesins
  - Toxins
  - Iron acquisition
  - Lipopolysaccharide (LPS)
  - Polysaccharide capsule
  - Invasins
- Classification:
  - Presence of antigen: *Escherichia coli* can be classified on the bases of serotype.
    - Somatic antigen present on the cell membrane is designated by a letter "O."
    - Antigen present on the capsule is represented by a letter K. Similarly, antigens located on fimbria are F and H antigens on bacterial flagella.
    - Presence of these antigens makes the bacteria more virulent. For example, presence of K1 antigen is responsible for neonatal meningitis, and the presence of 0157:H7 is associated with hemorrhagic colitis, hemolytic uremic syndrome (HUS), and diarrhea.
    - There are about 200 serotypes.
  - *E. coli* can also be classified on the basis of phenotypes.
    - Enterotoxigenic (ETEC) → toxin causes travelers diarrhea and watery diarrhea in infants. Does not cause blood in the stool.

    - Enteroinvasive (EIEC) → inflammatory diarrhea ± bloody diarrhea.
    - Enterohemorrhagic or Shiga-like toxin-producing *E. coli* (EHEC or STEC) → serotype 0157:H7 cause bloody diarrhea and Hemolytic Uremic Syndrome (HUS)
    - Enteroaggregative → persistent diarrhea in AIDS patients.
    - Enteropathogenic (EPEC) → watery diarrhea in infants and children.
    - Uropathogenic *E. coli* (UPEC). Cause urinary tract infection (UTI).
- Clinical significance:
  - UTI → *E. coli* is the most common cause.
  - Gastroenteritis
  - Extraintestinal
    - Cystitis (most common)
    - Bacteremia
    - Meningitis → especially in infants
    - Skin, pulmonary, peritoneal, and hepatobiliary infections
  - Diagnosis:
    - Stool/blood/urine culture on sorbitol-MacConkey agar
    - PCR
  - Choice of antibiotics:
    - First choice: third or fourth generation cephalosporin
    - Second choice: ciprofloxacin or levofloxacin
    - Extended-spectrum beta-lactamase (ESBL)-producing *E. coli* → meropenem or ertapenem
    - Resistance to meropenem → ceftazidime–avibactam or meropenem-vaborbactam
    - Fosfomycin for cystitis or lower UTI
    - TMP-SMX for UTI outpatient

4.3.1.1.1.2 Klebsiella pneumoniae, *Serratia, and Enterobacter*

- Closely related to each other.
- Infect hospitalized patients or patients with a decreased immune system.
- Encapsulated, nonmotile enteric.
- Virulence factors:
  - Capsule
  - Lipopolysaccharides (LPS)
  - Siderophore
  - Fimbriae
  - Biofilm
  - Antibiotic resistance
- Clinical significance:
  - Sepsis
  - UTI in a patient with Foley catheters
  - Pneumonia in hospital and alcoholic patients

  - Klebsiella → characteristic "red currant jelly" sputum, which is the color of O antigen capsule
  - Produce lung cavity and lung abscess
  - Serratia → mostly causes UTI and produces a bright red pigment
  - Enterobacter → nosocomial infections, otitis media, cellulitis, and neonatal sepsis
- Choice of antibiotics:
  - First choice: third or fourth generation cephalosporin or fluoroquinolones. Second choice: piperacillin-tazobactam or aminoglycoside
  - ESBL-producing strain → meropenem or ceftazidime-avibactam
  - Carbapenemases-producing strain → ceftolozane-tazobactam, ceftazidime-avibactam, or meropenem-vaborbactam

4.3.1.1.2 Nonlactose fermenting

- These are not part of human intestinal flora but reside in the gut of animals such as chickens, eggs, pigs, turtles, snakes, fish, and other species.

4.3.1.1.2.1 Salmonella

- Facultative intracellular bacteria produce H_2S on triple sugar agar
- Have several serotypes. Each strain is associated with a different type of infection. Broadly classified into:
  Salmonell typhi → causes typhoid fever.
  Nontyphoid Salmonella → gastroenteriti

a) Salmonell typhi

- Serotype *S. typhi*.
- Human is the only host and reservoir. Shed in stool or urine of asymptomatic carrier or patients with disease.
- Bacteria enter water or food through feces or urine due to unhygienic conditions and infect other people.
- From the gut, it reaches to the lymphatic system and bloodstream and causes typhoid fever.
- Endemic to Asia, Africa, Latin America, and the Caribbean.
- Virulence factors:
  - Facultative intracellular
  - Vi capsular polysaccharide antigen → protect the bacteria from being tagged with antibodies.
  - Type III secretion system (T3SS) → prevent vacuole fusion with the lysosome inside the phagocytic cells. This helps *S. typhi* to survive and replicate inside the vacuole.
  - Fimbriae
  - Flagella

- Clinical significance:
  - Typhoid fever
  - Sepsis
  - Osteomyelitis

Typhoid fever

- Incubation period is about 1–2 weeks, and symptoms may last 4–6 weeks. It could be life threatening if not treated.
- Sign and symptoms:
  - High-grade fever, headache, abdominal pain, constipation followed by diarrhea, and rose spots rash on the trunk.
  - Splenomegaly, hepatomegaly, hepatitis, cholecystitis, and proteinuria may develop.
  - Diarrhea with or without blood can develop.
  - Other complications are → pneumonia, bacteremia, endocarditis, meningitis, and glomerulitis.
- Diagnosis:
  - Clinical
  - Culture
  - Serology test → Widal test: Detects antibodies against the O and H antigens of *S. typhi*.
- Treatment:
  - Mortality is high without treatment
  - First choice: Ceftriaxone, azithromycin, or meropenem (severe)
  - Second choice: Fluoroquinolone or chloramphenicol
  - Resistance is high and follows susceptibility test
- Carrier state:
  - About 3% of patients who are not treated enter into chronic carrier state and harbor bacteria in their gallbladder. Some people with no clinical symptoms are silent carriers and shed the bacteria in the stool.
  - Use fluoroquinolone or surgery to remove the gallbladder.
  - Vaccine available containing inactive Vi capsular polysaccharide or live oral vaccine.

b) Nontyphoid salmonella

- Nontyphoid salmonella causes various types of infections that involve various serotype.
  - Bacteremia → prolongs fever, headache, malaise but usually no diarrhea. Bacteremia may lead to focal infection of the bone (osteomyelitis), heart (endocarditis), lungs, joints, soft tissue, and genitourinary tract.
  - Gastroenteritis → causes inflammatory diarrhea with mucus and blood, abdominal cramp, nausea and vomiting, headache, chill, and low-grade fever.

- Diagnosis is clinical. Culture can be done.
- Choice of antibiotic: usually avoided in uncomplicated gastroenteritis as it may prolong the excretion of bacteria. However, in high-risk patients or immune-compromised patients, antibiotics can be used.
  - Ciprofloxacin, azithromycin, and ceftriaxone are the first choice antibiotics.
  - Preventions → washing hands with soap and water and preventing contamination of the food and water supply.

4.3.1.1.2.2 Shigella

- Four species of Shigella cause shigellosis, which is an acute infection of intestine. Species involved are:
  - *Shigella dysenteriae*: Responsible for most severe form of shigellosis
  - *Shigella flexneri*
  - *Shigella boydii*
  - *Shigella sonnei*
- Facultative anaerobic, nonmotile, nonlactose fermenting, urease and oxidase negative, and does not produce H_2S.
- Spread via fecal oral route, contaminated food, and fomites.
- Human is the only natural reservoir, but the bacterium is not a part of normal flora of human intestine.
- Virulence factors:
  - Acid tolerance: Survive at low PH
  - Effector proteins:
    - Shigella uses number of effector proteins that bind to host cells and lyse the phagosome and release the bacteria into cell cytoplasm.
    - Plasmid antigen B (IpaB) binds to host cells and initiates a pathway to kill the microphages, while IpaC effector protein helps Shigella to move and spread within host cells.
  - T3SS: It is used to deliver effector protein in the host cytoplasm.
  - *S. dysenteriae* secrete toxin (Shiga toxin), which is very similar to EHEC and EIEC toxin.
  - Shiga toxin has two subunits, A and B. B subunits are used to bind to the host cell membrane, while subunits A cleave ribosome subunit 28S and result in cell death.
- Clinical relevance:
  - Acute symptoms of inflammatory diarrhea ± mucus and blood, abdominal cramp, tenesmus, mild fever, and the sign of dehydration
- Complications:
  - Hemolytic Uremic Syndrome (HUS)→ in children
  - Reactive arthritis → patients with HLA-B27 genotype

  - Seizure in children
  - Myocarditis
  - Intestinal perforation
- Diagnosis
  - Stool culture
- Treatment:
  - Supportive
  - Antibiotics
    - First choice: Azithromycin, fluoroquinolone, third generation cephalosporin, and levofloxacin
    - Second choice: Trimethoprim-sulfamethoxazole
    - Avoid the use of antidiarrheal drugs → prolong the illness

4.3.1.1.2.3 Yersinia enterocolitis

- Gram-negative, facultative anaerobic, and intracellular, nonspore-forming, non-oxidase producing bacteria grow well in MacConkey agar and form colorless colonies (nonlactose fermenter).
- Require iron for its survival.
- Can be motile @ 35°C and nonmotile @ 37°C.
- Animal feces contaminate food and water and are the source of infection.
- Virulence factors:
  - Produce enterotoxin similar to *E. coli*
  - Adhesins → YadA and Ail for attachment to gut epithelial cells
  - T3SS → blocks cytokines like IL-8 and TNF-alfa, inhibits activation of macrophages, and escapes from phagocytic cells.
- Clinical significance:
  - Acute enterocolitis with bloody diarrhea
  - Pseudoappendicitis
  - Septicemia
  - Postinfection sequelae: More often associated with HLA-B27 antigen.
    - Reactive arthritis
    - Erythema nodosum
- Antibiotics:
  - First choice: Ceftriaxone + tobramycin or fluoroquinolones
  - Second choice: TMP-SMX or doxycycline

4.3.1.1.2.4 Proteus mirabilis

- Part of normal fecal flora, also found in soil and water.
- Motile with swarming motility, nonlactose fermenting, urease-positive gram-negative bacilli.
- Bacterium has the ability to self-elongate and secrete polysaccharide when in contact with a solid surface. This helps the bacterium for attachment.

- Causes bacteremia, UTI, renal and bladder stone formation (struvite stone), pyelonephritis, mastoid sinuses, and peritonitis.
- Virulence factors:
  - Flagella
  - Fimbriae
  - Hemolysin → causes tiny holes in the cell membrane resulting in cell damage
  - ZapA protease → destroys IgA and IgG
  - Produces urease and ammonia, which alkaline the urine and causes precipitation of struvite (magnesium-ammonium phosphate and calcium carbonate-apatite) stone, and also increases the risk of UTI and pyelonephritis
  - Endotoxin
- Risk factors:
  - Old age
  - Hospitalized patients
  - Patient with catheter
  - Chronic kidney disease
  - Neurogenic bladder
  - Unprotected sex
- Clinical relevance:
  - Bacteremia
  - Urinary tract infection
  - Renal stone
  - Peritonitis
- Diagnosis:
  - Culture
  - Urine analysis
  - Gram staining and microscopic exam of a urine sample
- Choice of antibiotics:
  - Frist choice: Amoxicillin, amoxicillin-clavulanate, piperacillin-tazobactam, and third-generation cephalosporin
  - Second choice: TMP-SMX, ciprofloxacin or levofloxacin, meropenem, and cefepime

4.3.1.2 Vibrionaceae

- *Vibrio cholerae*
- *Vibrio parahaemolyticus*

- *Campylobacter jejuni*
- *Helicobacter pylori*

4.3.1.2.1 *Vibrio cholerae*

- Short, curved, comma-shaped, motile, gram-negative bacilli; produces toxins similar to *E. coli* and causes severe watery diarrhea.
- Bacteria is transmitted by the fecal oral route and contaminates the water supply or seafood.
- Endemic in many parts of the world.
- Virulence factors:
  - Flagella
  - Adherence factors
  - Produce enterotoxin choleragen that activates G-protein permanently and inhibits the reabsorption channels in the gut. This results in increased secretion of chloride, sodium, potassium, and bicarbonate in the lumen.
- Clinical relevance:
  - Responsible for watery diarrhea.
  - Symptoms start with rice water diarrhea, vomiting, no abdominal cramp, fever, and pain.
  - Loss of electrolytes, and dehydration results in oliguria, muscles cramp, hypovolemia, circulatory collapse, and death if not treated.
- Risk factors:
  - Poor sanitation
  - Close contact with the infected person
  - Patients with low gastric acidity
  - O-blood type happened to have more severe symptoms
  - Raw or undercooked shellfish
- Diagnosis:
  - Stool culture
  - PCR
  - Rapid dipstick test → low specificity
- Treatment:
  - Fluid and electrolyte replacement
  - First choice: Doxycycline or azithromycin
  - Second choice: TMP-SMZ or ciprofloxacin

4.3.1.2.2 Noncholera Vibrio infections

- *V. Parahaemolyticus*
- *V. mimicus*
- *V. hollisae*

} Diarrheal outbreak

- *V. alginolyticus*
- *V. vulnificus*

} ± diarrhea, infect wounds, associated with septicemia.

- Diagnosis:
  - Stool culture for enteritis and blood culture for septicemia or wound infections.
- Treatment:
  - Fluid replacement for enteritis.
  - First choice: Ciprofloxacin or doxycycline
  - Second choice: Third-generation cephalosporin + doxycycline for severe infection (CDC)

4.3.1.2.3 *Campylobacter jejuni*

- Gram-negative motile, curved or coma-shaped, oxidase-positive bacilli inhabit domestic animals' guts.
- Most common cause of bacterial gastroenteritis worldwide.
- Transmitted from animals to humans via fecal oral route, drinking unpasteurized milk, and eating raw or undercooked poultry.
- Children may get infected by playing with infected animals.
- Virulence factors:
  - Flagella
  - Fimbriae
  - Toxins
- Clinical relevance:
  - Cause watery diarrhea ± blood, abdominal pain.
  - Low-grade fever.
  - Incubation period is usually 1–7 days.
  - Patients may continue secret bacteria in the feces for several days after clinical improvement. However, patients receiving antibiotics less likely secrete the bacteria.
- Postinfection complications
  - Guillain–Barre syndrome
  - Reactive arthritis
  - Endocarditis
  - Meningitis
  - Fever of unknown origin
- Risk factors:
  - Young ages

  - Uncooked or undercooked poultry or meat
  - Unpasteurized milk
  - Contaminated water
  - Unhygienic condition
- Diagnosis:
  - Culture stool
  - Blood culture for extra enteritis
- Choice of antibiotics
  - First choice: Azithromycin
  - Second choice: Ciprofloxacin, doxycycline, and erythromycin

4.3.1.2.4 *Helicobacter pylori*

- Curved, microaerophilic, gram-negative bacilli. It is urease, oxidase, and catalase-positive.
- It is estimated that about 50% world's population is infected.
- Most people remain asymptomatic and are the silent carrier.
- Risk factors:
  - Low socioeconomic status
  - Overcrowding housing
  - Sharing bed
  - Lack of running water
  - Number of siblings
  - Unhygienic conditions
  - Salted food intake
- Transmission:
  - Fecal oral or oral to oral
  - Contaminated water supply
  - Eating uncooked vegetables
  - Use of inadequately disinfected medical devices such as endoscope
  - Iatrogenic
- Virulence factors:
  - Flagella
  - Adhesins
  - Urease → convert urea into carbon dioxide and ammonia and neutralize the acid.
  - Some strain carries a gene A or cagA that induce inflammatory response and cause gastritis
  - CagA is also linked to the development of gastric cancers (MALT lymphoma and adenocarcinoma).
  - Some *H. pylori* strain produces exotoxin (cytotoxin A), which destroys epithelial cells and exposes underlying mucosal layer to gastric acid.

- Clinical significance:
  - Cause duodenal ulcer, gastritis, gastric adenoma, and low-grade gastric adenoma.
  - Symptoms depend on where in the stomach the infection is?
  - Antral predominate causes increased gastrin production, which results in duodenal ulcer.
  - Body predominate causes gastric atrophy and ↓acid production, which result in gastric ulcer and gastric adenocarcinoma.
  - Chronic infection can lead to iron deficiency anemia.
- Diagnosis:
  - Urea breathe test → oral dose of urea with C 13 or C 14 is given. Bacteria metabolize urea and release label CO_2 that is exhaled by the patient and is measured. Sensitivity and specificity are greater than 95%.
  - The test is used to confirm the eradication of the bacteria after the therapy.
  - Stool antigen test → sensitivity and specificity are the same. Remain positive for a while, even after the treatment.
  - Endoscopy and biopsy.
- Treatment:
  - Quadruple therapy → proton inhibitor + bismuth subsalicylate + metronidazole + tetracycline
  - Nonbismuth regimen: Proton inhibitor + metronidazole + amoxicillin + clarithromycin
  - Triple therapy → Proton pump inhibitors + amoxicillin or metronidazole + clarithromycin
  - Multidrug resistance strain → protons pump inhibitor + rifabutin + amoxicillin
  - First treatment failure → repeat the therapy. Second treatment failure → endoscopy and culture for sensitivity

4.3.2 Hospital or nursing home acquired

4.3.2.1 Pseudomonas

- Opportunistic pathogens infect people with decreased immunity.
- Gram-negative, encapsulated, obligate aerobe, catalase, citrate, and oxidase positive bacteria.
- Love moist condition
- Account for approximately 10% of hospital-acquired infections.
- Second most common cause of hospital-acquired pneumonia.
- Risk factors:
  - Immunocompromised patients.
  - Patients with cystic fibrosis, diabetes, and granulomatous disease.
  - Patients with burn injuries, invasive devices, mechanical ventilation, or with other debility conditions.
  - Patients on broad-spectrum antibiotics or in ICU units.

  - IV drug abuser.
  - Use of contaminated whirlpools, spas, and swimming pools.
- Virulent factors:
  - Endotoxin → LPS.
  - Biofilm → shield the bacteria from immune cells.
  - Pili → adherence to epithelial cells.
  - Adhesins → adhesion to epithelial cells.
  - Exotoxin A → tissue necrosis.
  - Phospholipase C → thermolabile hemolysin. Degrades host cell membrane and causes lysis.
  - Exoenzyme S → responsible for the destruction of immunoglobulin IgG and IgA.
  - Proteases → tissue necrosis and bleeding.
  - Pyocyanin →blue pigment with sweet grape scent. It generates reactive oxygen and causes oxidative damage to host cells and death.
  - Pyoverdine → green pigment binds to iron and transports it into the bacterial cell.
  - Pseudo-capsule of alginate: protect the bacteria from phagocytosis.
- Clinical significance:
  - Pneumonia
  - Osteomyelitis
  - Wound infection especially burns wounds
  - Sepsis
  - UTI
  - Endocarditis
  - Malignant external otitis
  - Corneal infections
- Bacteria can infect any part of the body
- Resistance to many antibiotics
- Treatment:
  - Selection of antibiotics depends on the site of infection
  - External otitis → ciprofloxacin or polymyxin B irrigation or oral or Iv ciprofloxacin
  - Corneal infection → ciprofloxacin or levofloxacin or tobramycin eye drops
  - Systemic infection → ceftazidime, cefepime, carbapenem, meropenem monobactam, fluoroquinolone, and piperacillin-tazobactam
  - For ESBL → meropenem, ceftolozane-tazobactam or ceftazidime-avibactam.
  - Carbapenem resistance → ceftazidime-avibactam or meropenem-vaborbactam

4.3.2.2 Stenotrophomonas maltophilia

- Belong to the same group as *Pseudomonas aeruginosa*
- Resistant to Beta-lactam and carbapenems

- Cause pneumonia, and bacteremia in hospitalized immunocompromised patients
- First choice antibiotic:
  - TMP-SMX ± minocycline or levofloxacin
- Second choice:
  - Ceftazidime-avibactam + Aztreonam

4.3.2.3 Acinetobacter baumanni

- Obligate aerobe, oxidase negative, and nonlactose fermenting bacteria
- Commonly found in water and soil
- Cause hospital-acquired pneumonia, bacteremia, UTI, and infect Foley catheter
- Difficult to treat, multidrug resistance
- Antibiotics
  - First choice: Carbapenems, cefepime, ampicillin-sulbactam
  - Second choice: Aminoglycoside + fluoroquinolone or tigecycline or cefiderocol

4.3.3 Respiratory

4.3.3.1 Haemophilus influenzae

- Gram-negative, coccobacillus, nonmotile, facultative anaerobic bacteria, which is catalase and oxidase-positive.
- It grows on blood agar and chocolate agar with factors V and X.
- Part of normal flora in the upper respiratory tract and rarely causes disease.
- Incidence of *Haemophilus influenzae* infection is considerably decreased as a result of the vaccine. However, some cases still can be seen, especially in underdeveloped countries where vaccine is not routinely given.
- *H. influenzae* can be classified into encapsulated and nonencapsulated strains. Encapsulated strain is associated with several serious infections.
- *H. influenzae* has six serotypes → a to f, and several nonserotype strains.
- Serotype b causes most severe and invasive infections such as meningitis, bacteremia, pneumonia, septic arthritis, conjunctivitis, epiglottitis, and sinusitis
- Nontypable *H. influenzae* cause mucosal infections such as otitis media and sinusitis
- *Haemophilus aegyptius* cause purulent conjunctivitis and bacteremia
- *Haemophilus ducreyi* cause chancroid. Infect the people via skin abrasion
- Risk factors:
  - Age <5 years
  - No vaccination
  - No breastfeeding
  - Daycare
  - History of otitis media
  - Household smoking
  - Male gender

  - Contact with the infected person.
  - Native American
- Virulence factors:
  - Polysaccharide capsule
  - Biofilm
  - Pili
  - Endotoxin
  - Protease → destroy immunoglobulin IgA
- Clinical significance**:**
  - Meningitis
  - Bacteremia
  - Pneumonia
  - Septic arthritis
  - Conjunctivitis
  - Epiglottis
  - Sinusitis
- Antibiotics:
  - Depends upon the site of infections.
  - First choice: Third- or fourth-generation cephalosporins, amoxicillin-clavulanate
  - Second choice: Macrolide, levofloxacin, clarithromycin, or azithromycin
- Vaccine: Initially, when the vaccine was introduced, it was a polysaccharide vaccine with a main ingredient of purified polyribosyl ribitol phosphate (PRP), which is the main component of the bacterial capsule. It was thought that the antibodies against the PRP would be protective. However, it turned out that the immune response against PRP was not enough. B-cell recognized the PRP antigen, but the T-cells didn't. This resulted in an incomplete immune response with no long-term immunity. It was later found out that if PRP covalently linked to protein molecules, it will incite predicted immunological response. That is why vaccine is called a conjugated vaccine. Currently, HIB vaccine is a purified or synthetic PRP, which is conjugated with nontoxic mutant diphtheria toxin or tetanus toxoid or meningococcal outer membrane protein. In the United States, there are three monovalent conjugated Hib vaccine.
  - ActHIB (PRP-T) * PRP-T uses tetanus toxoid carrier protein
  - Hiberix (PRP-T) PRP-OMP uses meningococcal outer membrane
  - Pedvax (PRP-OMB) protein
  - Two combination vaccine:
    Pentacel
    Vaxelis
  - Vaccines are available for children for 2–6 months old and a booster at ages of 12–15 months.
  - Primary series of Hib (PRP-T) requires three doses, whereas Hib (PRP-OMP) requires two doses.

4.3.3.2 *Legionella pneumophila*

- Facultative intracellular bacteria, with oxidase and catalase positive, produce beta-lactamase.
- It resides in water, hot water tanks, cooling towers, large air-conditioning systems, and soil.
- In water, legionella grows and multiplies inside amebae, which provide nutrients and protection to the bacteria.
- Bacteria grow in a special medium called buffered charcoal yeast extract (BCYE), which contain cysteine and iron that are necessary for the growth of legionella.
- Bacteria enter the human body by inhalation, where they are engulfed by the macrophages. Inside the macrophages, legionella secretion systems prevent the fusion of phagosome with lysosomes, and legionella survives, thrives, and grows in numbers, bursts out and infects other cells.
- Chemokines and cytokines released by infected macrophages result in a strong inflammatory response and destruction of host cells.
- Risk factors:
  - Age >50 years
  - Smoking
  - Chronic lung disease
  - Immunocompromised
  - Underlying disease or malignancy
  - Recent travel with an overnight stay outside home
  - Exposure to hot tubs
  - Hospital or long-term care facilities stay
- Virulent factors:
  - LPS
  - Flagella
  - Pili
  - Outer membrane proteins → play an important role in phagocytic entry and survival.
  - Secretion systems → Legionella species have several pigments, toxins, enzymes, proteins, and type II (T2SS) and type IV (TIVSS) secretory system (T2SS), which are necessary for the survival and intracellular growth of the bacteria.
  - Biofilm
- Clinical relevance:
  - *Pontiac fever* → headache, fever, chill, malaise, fatigue, abdominal pain, and ± watery diarrhea.
  - *Legionnaires disease* → all symptoms of Pontiac fever + pneumonia and high fever.
  - Diagnosis:
    - Direct fluorescent antibody staining

  - Culture (sputum)
  - Rapid urinary antigen test
- Treatment:
  - First choice: Fluoroquinolone or azithromycin
  - Second choice: Doxycycline or clarithromycin

4.3.3.3 Bordetella pertussis

- Gram-negative, coccobacilli, nonmotile, encapsulated bacteria.
- There are several species of *Bordetella*. However, only *Bordetella pertussis* and *Bordetella parapertussis* species cause pertussis in human.
- Human is the only known reservoir for *B. pertussis*. Therefore, it is only transmitted from person to person.
- Bacteria have the propensity for ciliary epithelium of the respiratory tract.
- Virulence factors:
  - Filamentous hemagglutinin → helps the bacteria to anchor on to the epithelia and has hemagglutinating activity.
  - Lipopolysaccharide (LPS)
  - Tracheal cytotoxin → paralyzes and destroys the cilia.
  - Heat labile toxin → produces strong vasoconstrictive effects.
  - Pertussis toxin → agglutinates red blood cells (RBCs), increases lymphocytes, stimulates T cell division, and increases the sensitivity of the blood vessels and respiratory tissue to histamine. This makes the airways swell up.
  - Adenylate cyclase toxin → blocks the oxidative response of phagocytic cells and natural killer cells.
- Risk factors:
  - Infants
  - Nonimmunized children
  - Adults >65 years
  - Comorbidity like asthma and COPD
  - Obesity
- Clinical relevance:
  - Responsible for pertussis

Pertussis (whooping cough) (Table 4.2)

- Highly contagious
- Transmission
  - Direct inhalation of aerosolized droplets from infected patients
  - Contacting mucosal discharge
  - Touching the contaminated surfaces and then touching the eyes and nose → rare
- Three phases → 1 or 2 weeks long
  1. Catarrhal phase: Initial phase lasts 1–2 weeks.
     - Malaise, rhinorrhea, mild cough, excessive lacrimation, and conjunctival injection
     - Contagious phase

2. Paroxysmal phase:
- Starts with second week
- Lasts 1–6 weeks and may last up to 6 weeks
- Paroxysmal cough (forceful cough) in series followed by loud whooping sounds as inhalation from the partially closed airway, posttussive emesis, cyanosis, and exhaustion
- Worse at night

3 Convalescent phase:
- Cough decrease in severity and frequency
- Lasts 1–2 weeks or longer
- No longer contagious
- May recur for months

- Communicable period: Catarrhal stage plus first 2 weeks after onset of cough. Patient is usually not infectious after third week of the paroxysmal phase
- Complications:
  - Asphyxia in infants
  - Otitis media
  - Pneumonia
  - Seizure in young children
  - Brain, eye hemorrhages due to paroxysmal cough
  - Umbilical and rectal prolapse
- Diagnosis:
  - Nasopharyngeal culture and PCR
  - Serological testing
- Treatment:
  - Isolation
  - Macrolide, if given in the catarrhal phase, decreases the severity of the symptoms. No effect if given after the catarrhal phase.
  - Infants may need to be hospitalized.
  - IV fluid, oxygen therapy as needed.
- Prevention: Tdap or Tdap vaccines
- Infection or vaccine does not result in lifelong immunity. Booster is needed every 8–10 years

Table 4.2 Comparison of croup and whooping cough.

	Croup	**Whooping cough**
Cause	Viral	Bacterial
Group	Infants, toddlers, and children	Infants, toddlers, children, and adults
Symptoms	Fever, barking cough, and hoarseness	Fever, forceful paroxysmal whooping cough, gasping air, malaise, and rhinorrhea
Duration	Week	Months
Treatment	Supportive	Supportive, antibiotic in catarrhal phase
Vaccine	None	TDap and Tdap

4.3.4 Zoonotic

These bacteria reside in wild animals and are transmitted to humans by fleas, ticks, or animal bites.

4.3.4.1 Yersinia pestis

- Gram-negative, bipolar staining (ends stained more than the center), resemble safety pin.
- *Yersinia pestis* is capsulated, catalase positive, citrate negative, and nonflagellated.
- Genus *Yersinia* has three important species that cause infection in humans. *Y. pestis*, *Y. enterocolitica*, and *Y. pseudotuberculosis*.
- *Y. pestis* infects wild rodents such as rats, mice, squirrels, and prairie dogs. Flea bites the infected rodents and becomes the carrier.
- Inside the flea gut, bacteria loss their capsule.
- Flea bites the human and spits the bacteria at the bite site. The bacteria enter the human host. However, most of the bacteria are killed by the host polymorphic cells, but some are survived and replicate inside the macrophages.
- Inside the macrophage bacteria reacquire the capsule.
- Infected macrophages migrate to lymph nodes, particularly inguinal or femoral lymph nodes and spread the disease.
- Bacteria kill the macrophages and are released into the extracellular environment and infect other organs.
- Lymph nodes get tender, firm, and massively swollen, called bubo.
- Virulent factors:
  - Capsule
  - T3SS → dampen the immune response by blocking the secretion of pro-inflammatory cells and inactivates fusion of phagosome and lysosome.
  - Siderophore called yersiniabactin captures iron molecule and essential nutrients for the *Y. pestis*.
  - Endotoxins → responsible for increased production of thrombin which causes procoagulant state and results in DIC, multiorgan infarct.
- Transmission:
  - Bite of rodent flea → most common.
  - Scratch or bite from the infected animal.
  - Inhalation of the respiratory droplet from infected animals.
  - Laboratory handling.
- Clinical relevance:
  - Responsible for plague. Pandemics “black death” in the 14th century in Europe and pandemic in the 19th century in Asia and India.

Plague (Fig. 4.1)**:**
Can be classified into:

- Bubonic plague: Most common form, manifested with fever and chills, large tender lymph nodes, usually inguinal or femoral lymph nodes, but other nodes can also be involved. Blackish discoloration of the skin is due to hemorrhages and is named "Black Death." Enlarge spleen and liver are common.
- Pneumonic plague: Bacteria reach the bloodstream, spread to the lungs, and cause pneumonic plague. Patients have high fever and cough with blood, pneumonia, and all other symptoms of bubonic plague.
- Septicemic plague: Infection spreads all over the body and results in DIC → gangrene in extremities and multiorgan failure. If not treated, death is imminent.

- Diagnosis:
  - Culture
  - Serological tests
  - PCR
- Choice of antibiotics
  - First choice
    - Streptomycin or gentamycin
  - Second choice
    - Doxycycline, ciprofloxacin, levofloxacin, or chloramphenicol
  - Prophylaxis: Doxycycline and ciprofloxacin. TMP-SMX for children.

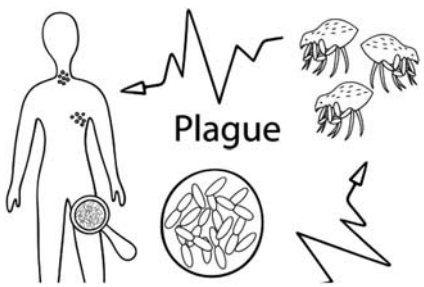

FIGURE 4.1 Plague.

4.3.4.2 Francisella tularensis

- Gram-negative, nonmotile, nonspore-forming, facultative intracellular, aerobic bacteria.

- It is oxidase and urease negative.
- It grows on cysteine-rich chocolate agar and BCYE agar.
- Cause tularemia which is similar to bubonic plague.
- Fleas, ticks, or deer flies are the carrier and infest on the blood of infected rabbits, hare, deer, and rodents and infect humans.
- It is also spread via contaminated water, food, inhalation, and direct contact with the infected specimen.
- Risk factors:
  - Veterinarians, zookeepers, and park rangers
  - People live in forest area
  - Hunters, taxidermists, and butchers
  - People work in gardening and landscaping
- Virulent factors:
  - Capsule
  - LPS is inactive, does not bind to Toll-like receptors 4 (TLR4) on immune cells, hence does not activate the innate immune system.
  - Type IV pili for attachment.
  - Acid phosphatase → prevents the fusion of phagosome with the lysosome.
  - Produce siderophore → binds to iron and transport to the bacterial cell.
  - Facultative intracellular → replicates inside the macrophages, bursts out, and causes bacteremia.
  - Distribution area is in the United States (Midwest) and Europe.
  - Incubation period is 3–5 days.
- Clinical relevance:
  - Responsible for tularemia.

Tularemia

- Signs and symptoms:
  - Incubation period is 3–5 days up to 21 days.
  - Fever, chills, headache, nausea and vomiting, and regional lymphadenopathy.
  - Papules appear at the site of infections and get inflamed and ulcerated, usually painless.
  - Inhalation leads to pneumonic tularemia → dry cough, lung consolidation, fever, chills, headache, nausea, vomiting, and regional lymphadenopathy.
  - Splenomegaly may be present.
  - Complications → lung abscess, meningitis, septic shock, and multiorgan failure.
  - Diagnosis:
- Culture
- Serological tests
- PCR
  - Choice of antibiotics:
    - Frist choice

- ➢ Streptomycin or chloramphenicol
- ➢ Gentamicin
- Second choice:
  - ➢ Doxycycline
  - ➢ Ciprofloxacin

4.3.4.3 Pasteurella multocida

- Gram-negative, nonmotile, facultative anaerobic bacteria. It is oxidase and catalase positive. Reduced nitrate to nitrite.
- Grows at 37° on sheep agar, chocolate agar, Mueller–Hinton agar, or brain heart infusion agar.
- Pasteurella has several species. Most common is *Pasteurella multocida*.
- Grouped into five serotypes (A–F) depending upon the capsular antigen. Only serogroups A and D cause disease in human.
- Colonize in the mouth of cats, dogs, and other mammals.
- Transmission:
  - Bite or scratch of domestic animals.
  - Animal licking has also been associated with infection.
  - Human to human.
- Virulent factors:
  - Capsule
  - Fimbriae
  - LPS
  - Toxin → called pasteurella multocida toxin (PMT) causes damages to endothelial cells and edema, redness, and swelling.
- Clinical significance:
  - Cause wound infection following the bite of cats and dogs. Most of the bites involved have multiple pathogens such as staphylococci, streptococci, and anaerobes
  - Respiratory infection → pharyngitis, sinusitis, epiglottitis, otitis media, pneumonia, empyema, and lung abscess
  - Infectious arthritis and osteomyelitis
  - Meningitis, bacteremia, endocarditis, and intraabdominal infection
  - Infections are more severe in immune-compromised patients or patients with other comorbidities
- Diagnosis
  - Clinical
  - Wounds culture
  - X-ray
- Treatment
  - Debridement

- First choice antibiotics → amoxicillin-clavulanate or penicillin or cephalosporin or dicloxacillin
- Second choice:
  - TMP-SMX + clindamycin
  - Ciprofloxacin, levofloxacin, or moxifloxacin
  - Doxycycline

4.3.4.4 Bartonella species (Fig. 4.2):

- Gram-negative, pleomorphic, facultative intracellular pathogen preferably lives inside RBC and endothelial cells.
- Very slow growing bacteria.
- Poorly stained with gram stain. Directly visualized using silver nitrate-based Warthin–Starry stain.
- Found worldwide in a range of mammalian species.
- Cat flea, *Ctenocephalides felis*, serves as a vector for spreading the bacteria.
- Have several subspecies that cause infections in human.
- *Bartonella henselae* → cat is the primary reservoir and causes cat scratch disease and bacillary angiomatosis.
- *Bartonella quintana* → Human is the primary reservoir and causes bacillary angiomatosis.
- *Bartonella bacilliformis* → Oroya fever. Human is the primary reservoir.
- Virulence factors:
  - Invade RBC and preferably lives inside the RBC to evade the host immune system.
  - Use type IV secretory system (T4SS) that delivers toxins directly to the host cells.
  - Release bartonella effector proteins that stimulate erythrocyte production and damage other host cells.
  - LPS: Responsible for intense immune response.
- Clinical relevance:

Cat scratch disease

- Caused by cat scratch or bite
- Erythematous papule or pustule develops at the site of the scratch
- Regional lymphadenopathy, fever, malaise, and headache followed
- Complete recovery in 3–5 months except for patients with complications
- Complications:
  - Conjunctivitis with preauricular nodes
  - Encephalitis, seizure, unilateral vision loss, myelitis, and paraplegia
  - Culture negative endocarditis
  - Severe disseminated illness in immunocompromised patients
  - One third of cases of fever of unknown origin in children is caused by cat scratch disease

- Diagnosis:
  - Serological tests → titers
  - PCR
  - Biopsy and culture of nodules
- Choice of antibiotics
  - First choice: Doxycycline, azithromycin, rifampin, and gentamicin
  - Second choice: TMP-SMX, chloramphenicol, and ciprofloxacin

Bacillary angiomatosis

- Severe form of cat scratch disease.

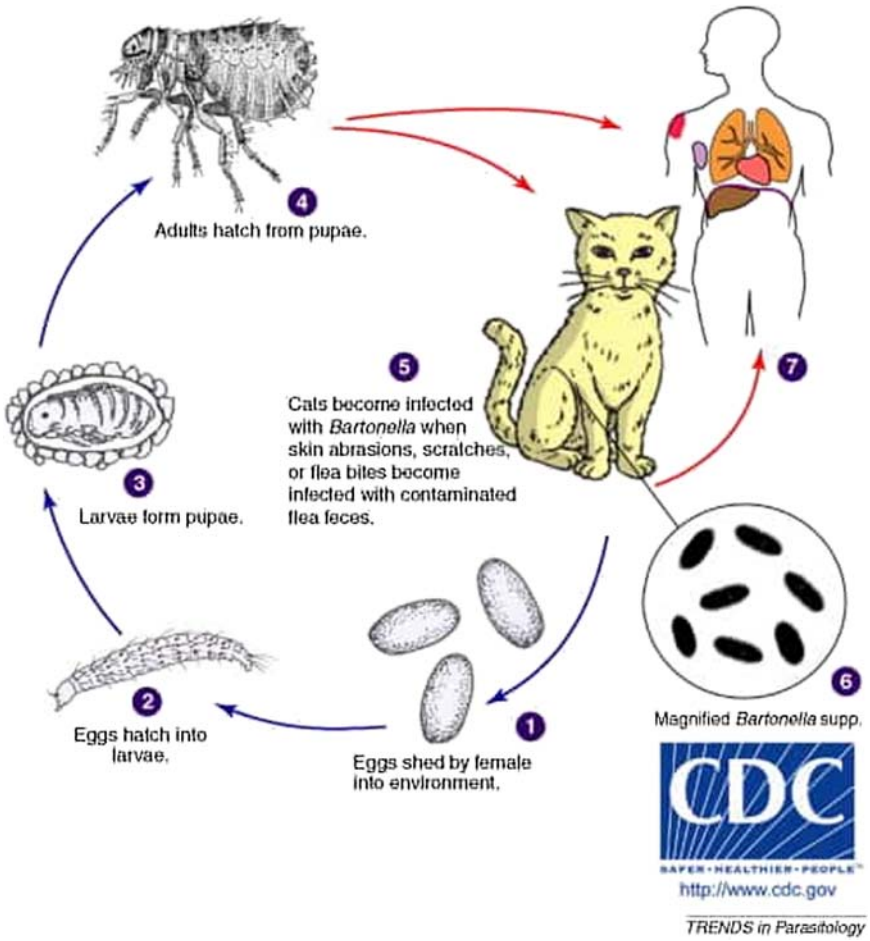

FIGURE 4.2 Life cycle of bartonella species.

- Immunocompromised patients are mostly affected.
- Red, raised berry-like nodules on the skin, which bleed easily and profusely.
- Looks similar to Kaposi sarcoma. The difference is that inflammatory cell mostly comprises neutrophiles, while in Kaposi's sarcoma, it is lymphocytes.
- Diagnosis
  - Biopsy and culture
  - PCR
- Treatment:
  - First choice: Erythromycin, doxycycline, and gentamicin
  - Second choice: Fluoroquinolone or TMP-SMX

Oroya fever
- Fever with profound hemolytic anemia
- Myalgia, headache, delirium, and coma
- Mortality >50%
- Treatment
  - First choice: Doxycycline, azithromycin, erythromycin, gentamicin, and rifampin
  - Second choice: Fluoroquinolone, TMP-SMX, and chloramphenicol

4.3.4.5 Brucella species
- Small, nonmotile, facultative aerobic, gram-negative, coccobacilli bacteria that grow very slowly. It required about 6 weeks of incubation.
- Cause brucellosis
- Several species involved infect different animals
  B. melitensis → goat
  B. abortus → cow
  B. suis → pigs
  B. canis → dogs
- Transmission
  - Direct contact with infected animal's secretions and excretions
  - Consuming raw milk, and undercooked meat of infected animals
  - Inhalation
  - Rarely person to person
  - Brucella can survive up to 2 days in milk at a temperature of 8°C, 3 weeks in frozen meat, and 3 months in goat cheese
- Virulent factors:
  - T4SS → secret several proteins that protect the bacteria from immune response and help the bacteria to travel to the endoplasmic reticulum, where it replicates in large numbers.
  - Nonendotoxic LPS prevents the fusion of phagosome with the lysosome.
- Clinical relevance**:**
  - Responsible for brucellosis.

Brucellosis

- Signs and symptoms:
  - Acute → sudden onset of fever with a headache, joint and low back pain, ± diarrhea, and night sweats.
  - Chronic → undulating fever, anorexia, weight loss, joint pain, headache, weakness, and granulomas in liver and spleen.
  - Complications → meningitis, encephalitis, endocarditis, cholecystitis, and orchitis.
  - Brucellosis in pregnancy may result in spontaneous abortion, intrauterine fetal death, premature delivery, or fetal infection.
  - Can infect any organ.
- Diagnosis
  - Culture → time consuming
  - Serological tests
  - PCR
- Choice of antibiotics
  - First choice: Doxycycline + rifampin or gentamicin or ciprofloxacin
  - Second choice: Streptomycin + doxycycline
  - Children <8 years old → SMZ-TMP + rifampin
  - Pregnancy: TMP-SMX + rifampin
  - Neurobrucellosis: Doxycycline + rifampin + ceftriaxone

4.4 Obligate intracellular bacteria

Obligate intracellular bacteria use host adenosine triphosphates (ATPs) for energy production. This class include the following bacteria.

- Chlamydia
- Rickettsia
- Coxiella

4.4.1 Chlamydia

- Gram-negative bacteria cannot retain pink safranin dye during gram stain because, unlike other gram-negative bacteria, it has no peptidoglycan in cell wall.
- Obligate intracellular, unable to make its own ATP for energy, nonmotile, and facultative anaerobe.
- Exist as two stages:
  a) Elementary bodies (infectious stage)
  b) Reticulate bodies (reproductive form)

- Taken by host cells as elementary body, which is a small spore-like inactive form of the bacteria. Inside the cell, it enclosed in a vacuole or inclusion where it coverts into active form called reticulate body.
- Reticulate body, which is a metabolically active form, multiplies many times by binary fusion and bursts out as elementary body from the host cell and taken by new cells.
- Genus Chlamydia consists of three species which include:

4.4.1.1 Chlamydia trachomatis

- Associated with various syndrome depending upon serotypes
- Serotypes A, B, and C cause trachoma, which is the infection of the eyes. Mostly in infants (keratoconjunctivitis) and is a leading cause of blindness worldwide
- Serotypes D to K are associated with nongonococcal cervicitis, urethritis, PIDs, and infant pneumonia
- Serotype L1 to L3 are associated with lymphogranuloma venereum
- *Chlamydia trachomatis* is the most common sexually transmitted disease worldwide. See detail in Chapter 10 under sexually transmitted diseases.
- Risk factors:
  - Unprotective sex
  - Sexually active before 25 years of age
  - Multiple partners
  - History of STD
- Virulence factors:
  - Intracellular pathogen
  - Polymorphic membrane D (PmpD) protein on the membrane acts as an adhesion molecule and helps entry into the host immune cells. PmpD also prevents fusion of phagosome with the lysosome.
  - Elementary body: Metabolically inactive and is the infectious form that develops into reticulate form in about 20 h inside of host immune cells.
  - Antigenic variation: There are about 15 serotypes. Antibodies developed for one type has no effects on another serotype.
- Clinical significance:
  - Keratoconjunctivitis
  - Nongonococcal cervicitis
  - Urethritis
  - PID
  - Pneumonia
- Choice of antibiotics:
  - First choice: Azithromycin
  - Second choice: Doxycycline, tetracycline, amoxicillin

4.4.1.2 Chlamydia psittaci

- Cause atypical pneumonia
- Infect birds and humans get infected by inhaling the bacteria from the dust, feather, and dried out bird feces

4.4.1.3 Chlamydia pneumoniae *serogroup TWAR*

- Atypical pneumonia

- Choice of antibiotics
  - First choice: Azithromycin or doxycycline
  - Second choice: Levofloxacin or clarithromycin

Differentiation of neonatal conjunctivitis

- Conjunctivitis on day first → silver nitrate reaction
- Conjunctivitis on days 2–5 → gonococcal infection gives ceftriaxone IV × 1 dose
- Conjunctivitis on days 5–14 → chlamydial infection → azithromycin po × 3 days
- Conjunctivitis on days 2–16 → HSV infection → start acyclovir IV or trifluridine
- Prophylaxis → erythromycin ophthalmic ointment at the time of birth for newborns

4.4.2 Rickettsiae

- Obligate intracellular, zoonotic bacteria require special staining such as Giemsa, Gimenez, or Macchiavello to visualize the bacteria.
- Infection is transmitted to humans by fleas, ticks, and mites.
- Tropism for endothelial cells that lined blood vessels.
- Risk factors:
  - Area around eastern United States
  - Campers
  - Inhabitants of wooded area
  - Wildlife workers
  - Traveler in endemic area
- Virulence factors:
  - Rickettsia uses outer membrane proteins called rOmps and SEPs for adhesion and entry into the host cells.
  - Inside the host cell, bacteria are trapped in the phagosome. However, it uses two enzymes, phospholipase D and tlyC to dissolve the phagosome membrane and enter into the cytoplasm where it divides by binary fission.
  - Then, bacteria invade the endothelial cells of blood vessels, resulting in cell damage and cell death. The inflammatory response followed, which causes edema, hypovolemia, hypotension, clogging of blood vessels, coagulopathies, decrease in platelets, and other clotting factors.
- Clinical relevance**:**
  - Most rickettsiae cause rash, fever, and headache.

- There are several species, but three are most common.
  - *Rickettsia rickettsii* → rocky mountain spotted fever
  - *Rickettsia prowazekii* → epidemic typhus
  - *Rickettsia typhi* →murine typhus.

Rocky mountain spotted fever (Fig. 4.3):

- Tick born infection, caused by *R. rickettsii* and transmitted by ixodid ticks.
- Most infections occurred in the Southeastern and Southcentral parts of the United States.
- Incubation period is usually 2−14 days.
- Fever, rash on the wrist, palms, soles, forearms, trunk, face, and other body parts. Other symptoms may include abdominal pain, joint pain, edema, bleeding, confusion, seizure, or focal neurological signs.
- Rash is blanching erythematous macules that change to petechial over time.
- Complications → encephalitis, hepatomegaly, hypotension, pneumonia, cardiac arrest, and death
- Diagnosis:
  - Clinical
  - Fluorescent antibodies test of rash biopsy
  - PCR
  - Culture in specialized laboratories
- Choice of antibiotics
  - First choice: Doxycycline
  - Second choice: Chloramphenicol
  - No vaccine is available
  - Doxycycline can safely be used in the pediatric population for <21 days).

FIGURE 4.3 Rocky mountain spotted rash. *Source: Wiki-commons.*

Epidemic typhus
- Worldwide prevalence
- Humans are the natural reservoir
- Transmitted by body lice
- Signs and symptoms are similar to other rickettsial diseases such as high fever, headache, and maculopapular rash. However, there is no rash on the sole and palm.
- Reoccurring of disease (Brill–Zinsser) in the milder form if the patient is not treated
- Complications, diagnosis, and treatments are the same for all rickettsial diseases.

Endemic typhus
- Transmitted by fleas.
- Less severe than epidemic typhus.
- Symptoms, diagnosis, and treatment are same.

4.4.3 *Coxiella burnettii*

- Intracellular, zoonotic, pleomorphic bacillus. Form endospores in unfavorable conditions such as in high temperature, dryness, digestive enzymes, and presence of antibiotics.
- *C. burnettii* does not grow in ordinary agar but requires special cell culture or embryonated eggs.
- Cattle, sheep, and goats are primary reservoirs.
- Transmitted by the inhalation of animal excretions or aerosolized spores.
- Occupational exposure is the most common form of acquisition.
- Risk factors:
  - Drinking unpasteurized dairy products
  - Eating contaminated meat.
  - Direct contact with the infected animal
  - Breathing dust contaminated with infected animal faces, urine, milk, and birth products
  - Veterinarians
  - Diary workers
  - Live stocks farmers
  - Researchers working with live stocks
- Virulence factors:
  - The bacteria are capsulated and express proteins called phase I and phase II antigens which are highly infectious.
  - The bacteria use T4SS and nonendotoxin LPS to survive from host immune cells and grow inside the macrophages and spread to other body organs.

- Clinical relevance
  - Responsible for Q fever

Q-fever

- Incubation period is typically 2–3 weeks after being exposed to the bacteria or spore.
- Initial symptoms start with influenza-like symptoms such as high fever, chills, sweating, headache, fatigue, dry cough, nausea, vomiting, and diarrhea.
- Symptoms can be mild and self-limited or severe which may include pneumonia or hepatitis.
- 5% of untreated patients may develop a chronic form. Symptoms include hepatitis or hepatomegaly, endocarditis, meningitis, and splenomegaly.
- Could be fatal if not treated.
- Diagnosis
  - Clinical
  - Immunofluorescence assay of infected tissue
  - Serological tests
  - PCR
  - Chest X-ray
- Choice of antibiotics
  - First choice: Doxycycline or TMP-SMX
  - Second choice: Fluoroquinolone, azithromycin, and clarithromycin.

4.5 Spirochetes

- Corkscrews-shaped gram-negative bacteria
- Cannot be cultured in ordinary media and cannot be seen in light microscope → too small except Borrelia, which can be seen in a light microscope
- Darkfield microscopy, immunofluorescence, and silver nitrate are used to identify
- Classified into three major groups or genera
  - Treponema
  - Borrelia
  - Leptospira

4.5.1 *Treponema*

T. pallidum → syphilis
T. endemicum → bejel

T. pertenue → yaws
T. carateum → pinta

- Risk factors:
  - Unprotected sex
  - Sex with known infected person
  - Previous history of syphilis or HIV
  - Born to an infected mother
  - Member of vulnerable population

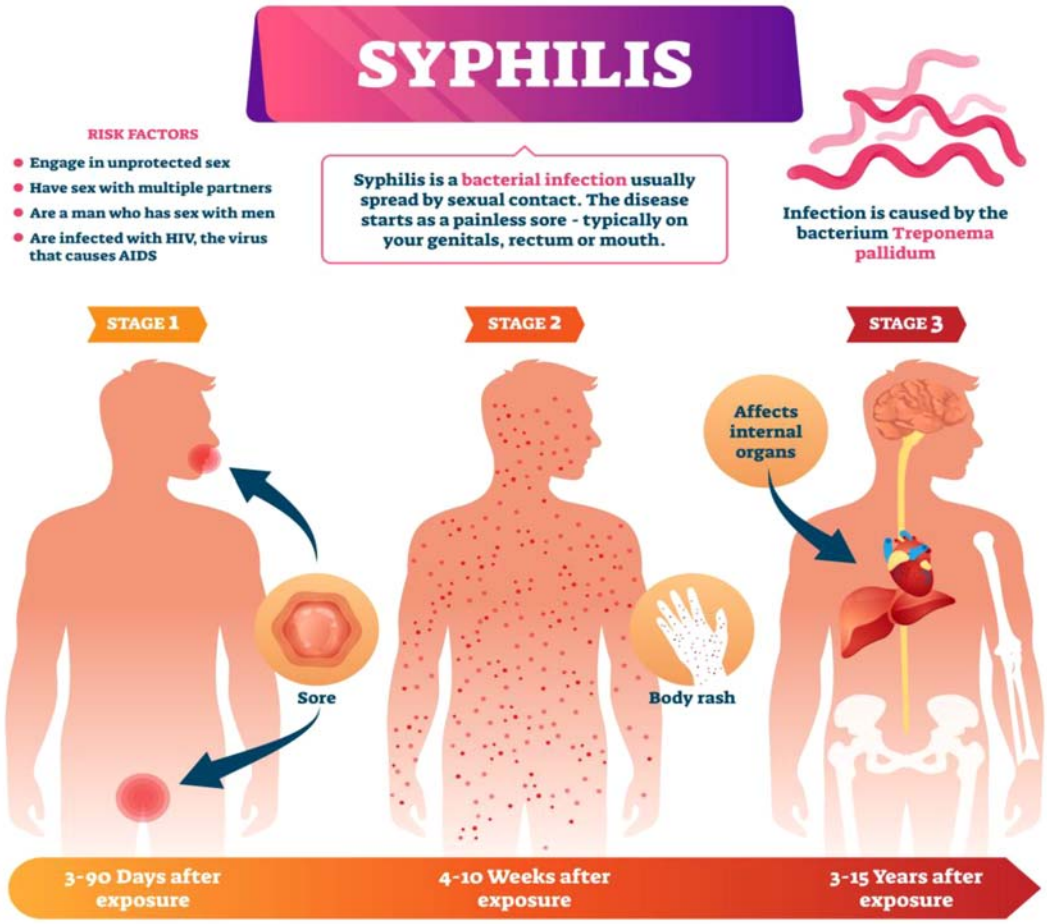
SYPHILIS
RISK FACTORS
Engage in unprotected sex
Have sex with multiple partners
Are a man who has sex with men
Are infected with HIV, the virus that causes AIDS
Syphilis is a bacterial infection usually spread by sexual contact. The disease starts as a painless sore - typically on your genitals, rectum or mouth.
Infection is caused by the bacterium Treponema pallidum
STAGE 1
STAGE 2
STAGE 3
Affects internal organs
Sore
Body rash
3-90 Days after exposure
4-10 Weeks after exposure
3-15 Years after exposure

FIGURE 4.4 - Syphilis.

Syphilis *(Fig 4.4)*:

Four stages

- Primary syphilis
- Secondary syphilis
- Latent syphilis
- Tertiary syphilis

Transmission

- Acquired syphilis
  - Sexual contact
  - Share contaminated needle
- Congenital syphilis
  - Infected mother transmits the infection to the baby either in the uterus or during vaginal delivery

Primary syphilis

- Painless chancre @ the site of inoculation. Usually, penis, rectum, vulva, cervix, lips, or mouth
- Nearby enlarged, painless, firm lymph nodes
- Heals in 3–12 weeks

Secondary syphilis

- 6–12 weeks after initial symptoms (chancre) in untreated patients
- Bactria spread all over the body and cause various symptoms depending upon the site involved
  - Skin: wide-spread rash, including on palm and sole. Condyloma lata → painless wart-like lesion on the moist area of skin such as perianal, vulva, under the breast
  - Lymph node: generalized lymphadenopathy. Lymph nodes are enlarged, non-tender, and firm
  - Other organs such as eyes, bones, meninges, kidney, liver, and spleen may also be involved

Latent syphilis:

- After secondary syphilis, patient enters into a latent phase
- Patients are asymptomatic during this phase, but serological test remains positive
- Although, some people (25%) may have relapses of symptoms during this phase
- Pregnant women can still transmit the infection to the fetus

Tertiary syphilis:

- Develops in 3–40 years after primary syphilis in 1/3 untreated patients

- Classified as:
  - Gummatous syphilis: Involves skin, bones and internal organs →localized granulomatous lesions grow and heal slowly. Skin lesions are usually painless, but the bone lesions cause deep pain, which gets worse at night
  - Cardiovascular syphilis: Involves:
    - Dilation of ascending aorta →aneurysm
    - Aortic valve insufficiency
    - Occlusion of coronary arteries
  - Neurosyphilis:
    - Asymptomatic neurosyphilis: Mild symptoms of meningitis. CSF analysis shows high lymphocytes count, high protein, low glucose, and positive syphilis test.
    - Meningovascular neurosyphilis: Inflammation of large to medium size arteries in the brain and spinal cord results in occlusion and infarct. Symptoms result due to neurological deficits.
    - Parenchymatous neurosyphilis: Causes inflammation or destruction of cortical parenchyma. Symptoms include behavior problem, irritability, dementia, headaches, seizure, hemiparesis, and other symptoms.
    - Tabes dorsalis: Degeneration of posterior columns and nerve roots in the spinal cord. Classical symptoms are → stabbing pain in the back and legs, loss of vibratory, proprioception senses, and reflexes in the lower extremities. Problem in gait, urinary retention, and incontinence. Patients may have Argyll Robertson pupils (ARPs).

ARP->pupils accommodate for near vision but do not respond to light

- Diagnosis:
  - Screening test → nontreponemal tests→ VDRL and RPR→ high sensitivity but not specific
  - Confirmatory test → treponemal tests include:
    - Fluorescent treponemal antibody absorption test (FTA-ABS)
    - Microhemagglutination assay for antibodies to *T. pallidum* test (MHA-TP)
    - *T. pallidum* hemagglutination assay (TPHA)
    - *T. pallidum* enzyme immunoassays (TP-EIA)
    - Tests remain positive for many years even after the treatment
    - Dark field microscopy: Most sensitive and specific for diagnosis in active lesion
    - PCR
- Treatment:
  - First choice: Benzathine penicillin G for all stages
  - Desensitize the patient if penicillin allergy in pregnant women
  - Second choice: Doxycycline, erythromycin, procaine penicillin G + probenecid, and ceftriaxone

Screening tests and confirmatory tests can be false negative if checked before three to six weeks of infection

Congenital syphilis

- Transplacental transmission of syphilis to the fetus
- There is about a 60%–80% chance that the infected mother transfers the infection to the fetus, especially in second trimester
- Transmission: ↓to 20% in latent or tertiary syphilis
- Classified into
  - Early congenital syphilis → birth–2 years of age → characteristic skin lesions including on palm and sole, generalized lymphadenopathy, snuffles (mucopurulent or blood-stained nasal discharge), hepatosplenomegaly, failure to thrive, meningitis, hydrocephalus, seizures, and developmental delay
  - Late congenital syphilis → after 2 years of age → neurosyphilis same as in the adult. Interstitial keratitis results in corneal scarring and rarely optic atrophy, leading to blindness. Hutchinson incisors (upper central incisors are widely spaced with central notch. Fig. 4.5), mulberry molars (molars have many cusps), bulldog face (maldevelopment of maxilla), and saber shins (osteoperiostitis of the tibia)
  - Diagnosis and treatment: Same as for adult

FIGURE 4.5 Hutchinson's teeth.

Bejel, pinta, and yaws:

- Similar to syphilis, starts with a mucocutaneous lesion, which later develops to secondary, latent, and destructive phase.

- They all spread with close contact. Bejel infection occurs in a hot and dry region of the eastern Mediterranean and Saharan West Africa. It starts with mucous membrane and cutaneous lesions and later spreads to bone and skin gummas.
- Yaws occur in humid equatorial countries. It involves dermal lesions and periostitis.
- Lesions in pinta are restricted to dermis. More common in Mexico and Central and South America.
- Diagnosis:
  - Clinical and epidemiological
  - Serological tests
  - PCR
- Treatment:
  - First choice: Penicillin → Benzathine penicillin G
  - Second choice: Azithromycin or doxycycline

4.5.2 *Borrelia species*

- Borrelia burgdorferi is the only species of spirochete responsible for tick-borne disease in the United States. However, in Europe, there are four other species besides *B. burgdorferi* that are responsible for tick-borne diseases.
- White-footed mouse and other rodents are the reservoirs, and Ixodes tick (Fig. 4.6) is a vector to spread the infection in humans.
- Area involves in the United States are Northeast, Midwest, and northwestern.
- Virulence factors:
  - Specific virulence factors for *B. burgdorferi* are not known; however, factors that most of the spirochaete share are:
    - Motility: Extremely fast motility allows the organism to escape from macrophages.
    - Adhesins.
    - Lipoprotein OspC: Use plasminogen to digest fibrin and large glycoproteins.
    - Chemotaxis system such as CheA and CheY helps the pathogen to chemotaxis favorably
- Clinical relevance:
  - Responsible for:
    - Lyme disease
    - Relapsing fever

Lyme disease

- Caused by *B. burgdorferi*
- Risk factors:

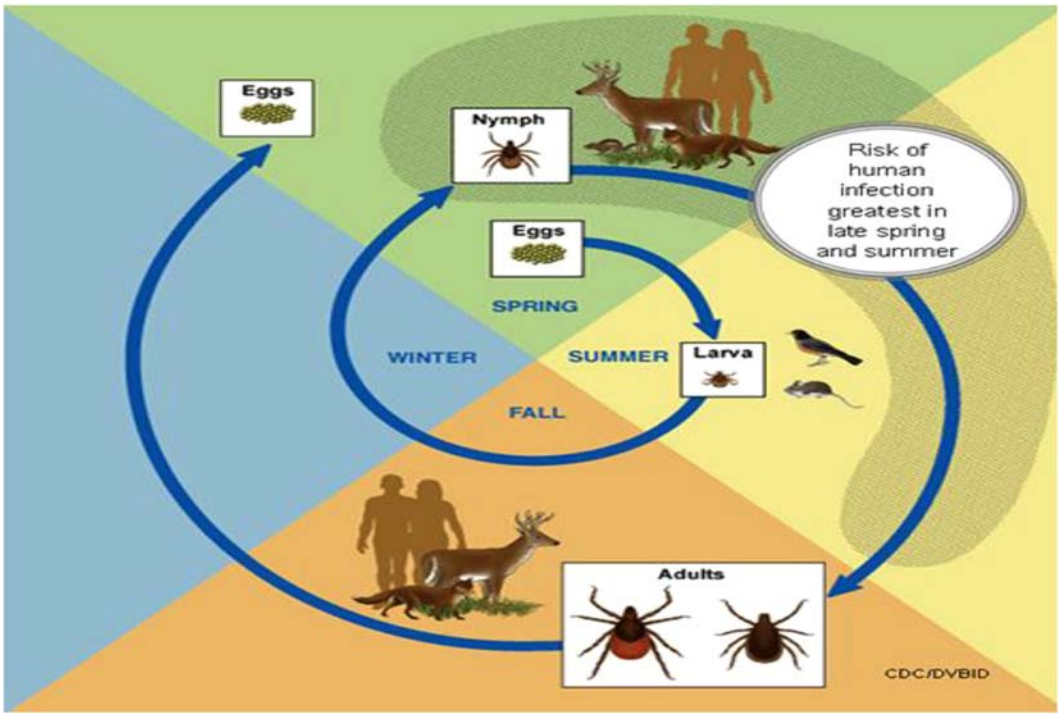

FIGURE 4.6 Life cycle of tick ixodes. *Source: CDC/DVBID.*

- *In the United States, Ixodes ticks or black-footed tick is mostly found in the Northeast and Midwest area. Spending time in wooded or grassy area increases the risk of tick biting.*
- *Tick has to attach on the skin for 36 to 48 h to transfer the spirochaete.*
- *Exposed skin*
- *Not removing the tick promptly or properly.*

- Sign and symptoms → three stages
  - Stage 1: Initial stage begins 1 or 4 weeks after the tick bite. Characteristic skin lesion appears at the site of bite called erythema chronicum migrans (ECM) or bull's eye (Fig. 4.7) rash along with flu-like symptoms and regional lymphadenopathy.
  - Stage 2: Spirochetes spread to other organs especially infecting skin, nervous system, heart, and joints. Skin→ multiple lesions similar to ECM. CNS → meningitis, cranial nerve palsies especially affect the seventh cranial nerve (bilateral bell palsy), and other neuropathies. Heart→ AV block, myocarditis, and LV dysfunction. Joints → migratory joint and muscles pain, large joints are swollen, hot, and painful.

    - Stage 3: About 10% of untreated people reached to third stage which is manifested with chronic arthritis, neurological sequelae such as impaired memory, encephalopathy, irritability, and insomnia.
  - Diagnosis:
    - Clinical
    - Serological tests
  - Choice of antibiotics
    - First choice: Doxycycline
    - Second choice: Ceftriaxone or amoxicillin

FIGURE 4.7 Erythema chronicum migrans.

Relapsing fever

- Relapsing fever is caused by several species of Borrelia. Most common is *Borrelia recurrentis.*
- Transmission
  - Body louse borne: When the infected louse is crushed, spirochete *B. recurrentis* released and penetrate the skin or enter via abraded skin.
  - Tends to occur in epidemics, especially in refugee camps and war-torn areas.
  - Tick borne: Endemic in Africa, Asia, America, and Europe. Rodents are the reservoirs and ticks get infected by sucking the blood of infected rodents.
- Sign and symptoms:
  - Incubation period is 3–11 days.
  - Start with fever followed by afebrile period of one week.

  - Fever returns after one week of the afebrile period. Symptoms are less severe after each relapse.
  - Other symptoms: erythema multiform (EM), severe headache, tachycardia, nausea, vomiting, muscles or joint pain, jaundice, hepatomegaly, splenomegaly, and meningitis,
- Diagnosis:
  - Clinical
  - Darkfield microscopy
  - Serological tests
- Choice of antibiotics
  - First choice: Doxycycline, tetracycline, and erythromycin
  - Second choice: Ceftriaxone → children or adults

Jarisch—Herxheimer reaction
- Can occur within 2—12 h of starting antibiotics.
- Exacerbation of symptoms such as fever, headache, malaise, and anxiety.
- Exact cause is not known, however, mistakenly diagnosed as an allergic reaction.
- Acetaminophen given before the start of antibiotics lessened the symptoms.

4.5.3 *Leptospira species*

- Gram-negative, motile, nonspore-forming, and aerobic bacteria.
- Have several serogroups. Most common is *Leptospira interrogans*, which is tiny, motile, spiral bacteria that can be visualized in darkfield microscope with immunofluorescence.
- Found in the urine of dogs, rats, and other wild animals.
- Humans are infected by direct contact with the urine of infected animals or indirectly from contaminated soil or water resources. Bacteria enter into the host system via abrasions or cut on the skin.
- Virulent factors:
  - Toxins
  - LPS
  - Adhesins
  - Sphingomyelinase C → toxin destroys RBCs and capillaries. Causes hemorrhage.
- Clinical significance:

Leptospirosis
- Sign and symptoms:
  - Biphasic symptoms
  - First phase or septicemic phase (4—9 days), nonspecific flu-like symptoms such as sudden fever, headache, muscles aches, cough, and hemoptysis. Classic

symptom of conjunctival effusion usually appears third or fourth day. Hepatomegaly and splenomegaly are common.
  - Second phase or immune phase → correlates with the appearance of IgM antibodies, and symptoms depend on the organ affected. Patient develops meningitis plus all other symptoms of septicemic phase. Lungs may be involved and cause severe pulmonary hemorrhages; kidney may be involved and result in kidney failure.
  - Well syndrome →A severe form of leptospirosis manifested by jaundice, renal failure, hepatitis, multiorgan hemorrhages, and thrombocytopenia. Mortality is up to 40% and is higher in older patients ages >60.
- Risk factors:
  - Contact with the urine of infected rodents, cats, and dogs.
  - Farmers, mine workers, sewer workers, slaughterhouse workers, and dairy workers.
  - Swimming, kayaking, and rafting in contaminated waters.
  - Flood.
- Diagnosis:
  - Clinical
  - Serological
  - Culture
  - PCR
  - Lumbar puncture if meningeal signs are present
- Choice of antibiotics
  - First choice: Doxycycline or penicillin G
  - Second choice: Ceftriaxone or azithromycin

Rat-bite fever

- Caused by:
  Streptobacillus moniliformis → US and Europe
  Spirillum minus → Asia
- Reservoir → healthy rats or mouse
- Transmission: Bite of a rat, ingestion of unpasteurized milk contaminated by *S. moniliformis*
- Sign and symptoms:
  - Sudden onset of viral-like symptoms with fever, nausea and vomiting, headache, joint and back pain. Fever comes and goes for months
  - Complications: Endocarditis, septic arthritis, and brain abscess
- Diagnosis:
  - Clinical
  - Culture
- Direct visualization of Spirillum in blood or tissue sample
- Choice of antibiotics

- First choice: Amoxicillin-clavulanate, doxycycline, or penicillin G
- Second choice: Erythromycin or clindamycin

4.6 Acid-fast bacteria

These bacteria are called acid fast because they have a physical property to resist in decolorization by acid during staining process. These bacteria have high content of mycolic acid in their cell wall, which retain red color dye during the laboratory staining process.

Includes:

- *Mycobacterium tuberculosis*
- *Mycobacterium avium*
- *Mycobacterium leprae*

4.6.1 *Mycobacterium tuberculosis*

- Responsible for tuberculosis (TB)
- Gram-negative, lipid rich wall, acid-fast bacilli
- Transmission → inhalation of airborne particles with bacteria
- Risk factors:
  - Environment → infected untreated people disperse the bacteria in the surrounding, overcrowded, and poorly ventilated areas.
  - People living in poor or underdeveloped areas.
  - Health care providers who take care of patients with active disease.
- Sign and symptoms—three stages
  - Primary infection
  - Latent infection
  - Active infection (Fig. 4.8)
- Primary infection
  - Usually asymptomatic and noninfectious in adult immunocompetent people.
  - In children and immunocompromised patients, primary infection may progress to acute illness.
  - Inhale bacteria are engulfed by alveolar macrophages, where it survives by inhibiting the fusion of phagosome with lysosome. Bacteria multiply inside the macrophages and burst out, destroying the cell.
  - Other inflammatory cells attract the area and wall off the bacteria called caseous granulomas or tubercles.
  - Tubercles calcified in the middle or lower zone of lungs called Ghon focus.
  - Ghon focus with perihilar lymph node called Ghon or Ranke complex.

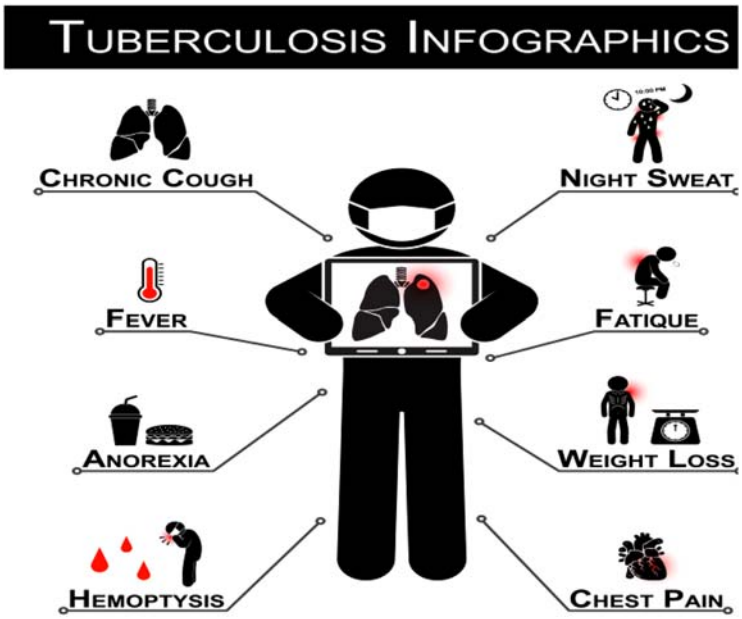

FIGURE 4.8 Sign and symptoms of tuberculosis.

- Latent infection:
  - Organisms remain dormant and survive for years in these tubercles and reinfect the person as immunity decreases.
  - Chance of reactivation is 10% in the lifetime of a common person.
- Active infections: (Fig. 4.8)
  - Tuberculosis can affect any organ in the body. However, most common organ affected is lung.
  - Pulmonary tuberculosis → most common symptom is cough. Hemoptysis occurs in cavitary TB. Other symptoms are anorexia, fatigue, weight loss, night sweating, and low grades fever.
  - Extrapulmonary TB:
  - Pleural/pericardial TB → results in fluid accumulation around the lungs and heart.
  - Lymph node TB → called scrofula.
  - Skeleton TB → Pott's disease.
  - CNS TB → subacute meningitis and granulomas.
  - Miliary TB → disseminated tubercules all over the body. Kidney, liver, lungs, and skin are all affected.

N-95 mask cannot filter out oil, but does filter 95% of aerosols.
N for not resistant to oil.

- Diagnosis:
  - Screening → purified protein derivative (PPD) skin test
  - Diameter of induration measured 48−72 h after subcutaneous PPD injection.
    - 5 mm → high-risk patients such as patients with HIV, immunosuppressive, and evidence of past TB.
    - 10 mm → some risk factors such as IV drug users, immigrants from the area with high prevalence of TB. Diabetic and kidney disease patients.
    - 15 mm → no risk factor.
  - IGRA (interferon gamma release assay): More specific and does not show a positive result in case of BCG vaccine.
  - Chest X-ray→ Characteristic multinodular infiltrate above or behind the clavicle. Middle and lower lungs infiltrate and calcified hilar nodes strongly suggest TB but are nonspecific.
  - Sputum culture or bronchoalveolar lavage → diagnostic, it may take up to three months for the final result.
  - NAAT → diagnostic.
- Treatment:
  - First-line treatment → isoniazid + rifampin × 6−9 months + pyrazinamide × 2 months + ethambutol × 2 months.
  - For isoniazid-resistant strain → rifampin + pyrazinamide + ethambutol + levofloxacin or moxifloxacin × 6−9 months.
  - Pregnancy →INH + rifampin + ethambutol × 9 month.
  - Multidrug-resistant strain (MDR).
    - Bedaquiline + pretomanid + linezolid × 26 weeks.
    - Five drugs regimen → Levofloxacin or moxifloxacin + bedaquiline + linezolid + clofazimine + cycloserine or streptomycin or amikacin.
    - For latent TB: Nine month of isoniazid once daily.

Pyridoxin should be added to avoid neuropathy caused by INH

4.6.2 *Mycobacterium avium*

- Mostly infect immunocompromised patients.
- Lungs are the most common site infected.
- Productive cough ± hemoptysis, weight loss, and low-grade fever.
- Clarithromycin, azithromycin, rifabutin, or amikacin can be used to treat the infection.

4.6.3 *Mycobacterium leprae*

- Cause leprosy.
- Infect skin, peripheral nerves, and mucous membranes.
- Humans and armadillos are the reservoirs.
- Transmission
  - Person to person via nasal droplets and secretions.
  - Long-term close contact.
  - Casual touch does not transmit the disease.
- Classification:
  - Tuberculoid or paucibacillary form: Strong cell mediated response to limit the disease. Skin lesions are usually less than five, and no bacteria are found on sample obtained from the lesion.
  - Lepromatous or multibacillary form: Poor cell mediated response results in greater than six skin lesions with the presence of bacteria in the sample obtained from the lesions.
- Sign and symptoms:
  - Tuberculoid leprosy → few nonpruritic, hypoesthetic, and macular leprosy form rash. The area is numb because of the nerve damage.
  - Lepromatous leprosy: Severe form. Other areas such as the nose, kidney, face, eye, and testes beside skin are also affected. This results in gradual destruction of the affected area.
- Diagnosis:
  - Clinical
  - Microscopic exam of biopsy of the lesion.
  - PCR
- Treatment:
  - Tuberculoid → rifampin + dapsone × 12 months
  - Lepromatous → rifampin + dapsone + clofazimine × 12 months

4.7 Bacteria with no cell wall

- These bacteria are very tiny and have no cell walls, pleomorphic, and intracellular.
- Sterols are part of the cell membrane.

EM = polymorphous macule, papules with characteristic target lesions with minimal mucosal involvement. HSV is the most common cause. *M. pneumoniae* and fungal infection are also responsible

- Includes:
  - *Mycoplasma pneumoniae*
  - *Mycoplasma genitalium*
  - *Ureaplasma urealyticum*

4.7.1 - *Mycoplasma pneumoniae*

- *M. pneumoniae* is a tiny, pleomorphic bacteria with no rigid cell wall and cannot be gram stained. It is intrinsically resistance to beta-lactam antibiotic due to the absence of cell wall.
- Occurs worldwide and mainly affects children of ages 5–9 years old.
- Causes walking pneumonia (atypical pneumonia) and bronchitis in young adults, children, military recruits, and dormitory students.
- Also responsible for encephalitis.
- Erythema multiforme (EM) is a classic skin sign along with pulmonary symptoms.
- Associated with Guillain–Barre syndrome.
- Immunoglobulin IgM developed due to *M. pneumoniae* infection cross-react with antigen on RBC and cause them to agglutinate at 4°C.
- Hemolysis is present in 50% of cases due to immune mediated hemolysis.
- Acquired by Inhalation of droplets.
- Risk factors:
  - Young children and older adults.
  - Immunocompromised people.
  - Patients with lung diseases.
  - People with sickle cell disease.
  - People on immunotherapy or chemotherapy.
- Virulence factors:
  - Tropism to the human respiratory and urogenital tract. Bacteria attach to tracheal epithelium via protein adhesin P1 and secret hydrogen peroxide and superoxide radicals to destroy the host cells.

  - Produce acquired respiratory distress syndrome (CARDS) toxin. The toxin aids the bacteria in colonization and also activates the host's inflammatory response.
  - Live and grow inside the host cells.
- Clinical relevance**:**
  - Responsible for atypical pneumonia
  - Signs and symptoms:
  - Nonproductive cough, fever, headache, and fatigue
  - Extrapulmonary symptoms: mild anemia, skin rash, EM, Steven Johnson syndrome, myalgia, and encephalitis
- Diagnosis
  - X-rays → patchy infiltrate, look worse than actual clinical symptoms
  - Culture → sputum culture on Eaton's agar media
  - PCR
  - Cold agglutinin test
  - Complement fixation test
- Treatment
  - Since bacteria have no cell wall, B-lactam antibiotics do not work
  - First choice: Doxycycline or azithromycin
  - Second choice: Tetracycline or levofloxacin

4.7.2 *Mycoplasma genitalium*

- Cause nongonococcal urethritis in men and cervicitis and PID in women
- Diagnosis → PCR, culture is difficult
- Treatment → Doxycycline, azithromycin, and moxifloxacin

4.7.3 *Ureaplasma urealyticum*

- Part of normal flora of about 60% of healthy women
- Cause lower UTI and urethritis
- Diagnosis → break down urea and produce ammonia and carbon dioxide
- Treatment:
  Frist choice: Doxycycline
  Second choice: Azithromycin

4.8 Summary of gram-negative bacteria and choice of antibiotics

Pathogen	Disease	Antibiotic	
		First choice	**Second choice**
		Gram-negative cocci	
Neisseria Meningitides	Meningitis, sepsis, septic shock	Ceftriaxone + dexamethasone, penicillin G, IV Ampicillin	Meropenem, chloramphenicol, aztreonam
Neisseria Gonorrhea	Urethritis, cervicitis, conjunctivitis, PID, septic arthritis, epididymitis	Ceftriaxone + azithromycin, gentamicin + azithromycin, doxycycline	Spectinomycin + azithromycin
Moraxella Catarrhalis	Otitis media, pneumonia	Amoxicillin-clavulanate, cefuroxime	Azithromycin, TMP-SMX, cefprozil, cefdinir
Kingella sp.	Osteomyelitis, endocarditis bacteremia, septic arthritis pneumonia, meningitis	Penicillin G or cephalosporin iv, tetracycline, fluoroquinolones	TMP-SMX, erythromycin
Gram-negative bacilli			
Enterics			
Enterobacteriaceae			
Lactose fermenting			
E. coli	UTI, gastroenteritis, cystitis bacteremia, meningitis, hepatobiliary, peritoneal, lung, and skin infection	Third or fourth generation cephalosporin	Ciprofloxacin, levofloxacin, carbapenem, piperacillin-tazobactam
Klebsiella, Serratia, and Enterobacter	UTI, pneumonia, lung abscess otitis media, cellulitis neonatal sepsis	Same as above	Same as above
Nonlactose fermenting			
S. typhi	Typhoid fever, pneumonia bacteremia, endocarditis	Ceftriaxone, azithromycin, meropenem (sever infection)	Ciprofloxacin, chloramphenicol
Nontyphoid salmonella	Bacteremia, gastroenteritis with mucus and blood	Avoid for uncomplicated case Ciprofloxacin, azithromycin, ceftriaxone	TMP-SMX, meropenem
Shigella sp.	Diarrhea with mucus and blood hemolytic uremic syndrome in children	Azithromycin, ceftriaxone, ciprofloxacin, levofloxacin	TMP-SMX

Continued

—cont'd

Pathogen	Disease	Antibiotic	
		First choice	**Second choice**
Yersinia enterocolitis	Bloody diarrhea, septicemia pseudoappendicitis	Ceftriaxone + tobramycin, ciprofloxacin	TMP-SMX, doxycycline
P. mirabilis	Bacteremia, UTI, renal stone formation (struvite), peritonitis	Amoxicillin-clavulanate, piperacillin-tazobactam, ceftriaxone	TMP-ZMX, ciprofloxacin, levofloxacin meropenem, cefepime
Vibrionaceae			
Vibrio cholera	Watery rice diarrhea, NV	Doxycycline or azithromycin	TMP-SMX, ciprofloxacin
Noncholera vibrio infection	Diarrhea, wounds infection, septicemia	Doxycycline, ciprofloxacin,	Azithromycin, doxycycline + ceftriaxone
C. jejuni	Diarrhea ± blood	Azithromycin	Ciprofloxacin, doxycycline, Erythromycin
H. pylori	Duodenal ulcer, gastritis gastric adenoma	Proton inhibitor + subsalicylate + metronidazole + tetracycline	Proton inhibitor + amoxicillin or metronidazole + clarithromycin
Bacteroidaceae			
B. fragilis	Intraabdominal infection	Metronidazole, piperacillin-tazobactam	Meropenem, amoxicillin-clavulanate
Hospital or nursing home acquired			
Pseudomonas	Pneumonia, osteomyelitis, sepsis, wound infection, endocarditis, malignant external otitis, corneal infection	Piperacillin-tazobactam, ceftazidime, meropenem, cefepime	Ciprofloxacin, levofloxacin, tobramycin, gentamycin, meropenem-vaborbactam, ceftazidime-avibactam
Stenotrophomonas maltophilia	Pneumonia in hospitalized patients mostly immunocompromised	TMP-SMX ± minocycline or levofloxacin	Ceftazidime-avibactam + aztreonam
Acinetobacter sp.	Pneumonia, bacteremia, UTI, infect Foley catheters	Meropenem, gentamycin, cefepime, ampicillin-sulbactam	Ciprofloxacin, levofloxacin, TMP-SMX, cefiderocal
Respiratory			
H. influenza	Meningitis, bacteremia, pneumonia, septic arthritis, conjunctivitis, epiglottis, and sinusitis	Ceftriaxone, cefepime, amoxicillin-clavulanate	Azithromycin, levofloxacin, clarithromycin
L. pneumophila	Pontiac fever, legionnaires disease	Levofloxacin, azithromycin	Clarithromycin, erythromycin, doxycycline
B. pertussis	Whooping cough (pertussis)	Azithromycin, clarithromycin	TMP-SMX

Zoonotic			
Y. pestis	Plague	Streptomycin or gentamicin	Doxycycline, ciprofloxacin, levofloxacin, TMP-SMX
F. tularensis	Tularemia	Streptomycin, or gentamicin, chloramphenicol, TMP-SMZ	Doxycycline, ciprofloxacin
Bartonella sp.	Cat scratch disease, oroya, fever, bacillary angiomatosis	Doxcycline, azithromycin ± rifampin or gentamicin	Clarithromycin, TMP-SMX, chloramphenicol, ciprofloxacin
Brucella sp.	Fever, headache, joint, back, pain, anorexia, weight loss, meningitis, endocarditis cholecystitis	Doxycycline + rifampin or gentamycin or ciprofloxacin	Streptomycin + doxycycline, TMP-SMX + rifampin
Obligate intracellular			
C. trachomatis	Keratoconjunctivitis, nongonococcal cervicitis urethritis, PID, pneumonia	Azithromycin	Doxycycline, tetracycline, amoxicillin
Rickettsiae sp.	Rocky mountain spotted fever	Doxycycline	Chloramphenicol
C. burnettii	Q fever, hepatitis endocarditis, splenomegaly	Doxycycline, TMP-SMZ, azithromycin, clarithromycin	Fluoroquinolone, erythromycin
Spirochets			
T. pallidum	Syphilis	Penicillin G, for neurosyphilis, desensitize the patient	Doxycycline, tetracycline, ceftriaxone, procaine penicillin G + probenecid
T. endemicum	Bejel	Penicillin G	Azithromycin, doxycycline
T. pertenue	Yaws	Same as above	Same as above
T. carateum	Pinta	Same as above	Same as above
Borrella sp.	Lyme disease and relapsing fever	Doxycycline	Ceftriaxone, amoxicillin
Leptospira sp.	Leptospirosis	Doxycycline	Amoxicillin, azithromycin
S. moniliformia and *S. minus*	Rat-bite fever	Doxycycline	Penicillin
Acid-fast bacteria			
M. tuberculosis	Tuberculosis	INH + Rifa × 6–9 months + PYZ + ETHA × 2 months	Rifa + PYZ + ETHA + LEVO or MOXI x 6–9 months → INH resistance strain. Bedaquiline + pretomanid + linezolid, X 26 weeks for MDR strain

Continued

—cont'd

Pathogen	Disease	Antibiotic	
		First choice	**Second choice**
M. avium	Lung infection in immunocompromised	Clarithromycin + ETHA ± rifabutin. Clarithromycin → prophylaxis	Azithromycin + ETHA. Azithromycin → prophylaxis
M. leprae	Leprosy	Rifampin + dapsone × 12 months (tuberculoid)	Rifampin + dapsone + clofazimine X 12 month (lepromatous)
Bacteria with no cell wall			
M. pneumoniae	Atypical pneumonia	Azithromycin, doxycycline	Tetracycline, levofloxacin
M. genitalium	Nongonococcal urethritis, cervicitis, PID	Doxycycline, azithromycin	Pristinamycin
U. urealyticum	UTI, urethritis	Doxycycline	Azithromycin

ETHA, ethambutol; *Ery*, erythromycin; *INH*, isoniazid; *LEVO*, levofloxacin; *MOXI*, moxifloxacin; *PYZ*, pyrazinamide; *Rifa*, rifampin.

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5 Antibacterial drugs

5.1 Classification

- B-lactam
- Monobactam
- Lipoglycopeptide
- Linezolid
- Protein synthesis inhibitors
- 30s ribosomal subunit inhibitors
- DNA gyrase and topoisomerase inhibitors
- Folic acid metabolism inhibitors
- Metronidazole
- Miscellaneous

5.2 Beta-lactam

- Penicillin
- Aminopenicillin
- Beta-lactamase resistance penicillin
- Anti-pseudomonas penicillin
- Cephalosporin
- Carbapenem

Key Features

- Have beta-lactam ring
- Bactericidal, time-dependent killing
- Inhibit transpeptidase enzyme and inhibit cell wall synthesis
- No MRSA coverage except Ceftaroline
- SPICE-A organism can be resistance to all beta-lactam except Carbapenem
- Any beta-lactam can cause allergic reactions, including anaphylaxis, rash, interstitial nephritis, seizure, and gastrointestinal (GI) problems
- No activity against atypical intracellular bacteria

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MRSA = methicillin resistance *Staphylococcus aureus*

SPICE-A

Serreta, Pseudomonas/Providence, Indole +ve, Proteus, Citrobacter, Enterobacter, Acinetobacter

5.2.1 Antipseudomonas beta-lactam

- Ticarcillin, Piperacillin, Piperacillin-Tazobactam, Ceftazidime, Cefoperazone, Cefepime, Carbapenem except Ertapenem, and Aztreonam.
- Cross-sensitivity of PCN (PCN skin test) with cephalosporin and carbapenems is 1%–2%, respectively.
- Aztreonam has no cross-sensitivity with PCN. Except with Ceftazidime.

5.2.2 Common side effects of beta-lactam

- IgE-mediated allergic reactions
- Rash
- Diarrhea
- Renal toxicity
- High doses may cause seizures

5.2.3 Penicillin (PCN)

- Penicillin VK, Penicillin G benzocaine, and Penicillin G procaine.
- Bind to penicillin-binding protein (PBP), inhibit transpeptidase enzyme, and arrest cell wall synthesis.
- Activity against gram-positive (gm +ve) bacteria except penicillinase and oxacillinase-producing staphylococcus, penicillin-resistant *Strep. pneumococci*, and some enterococci.
- Drug of choice for Group-A strep, most oral anaerobes, and syphilis.
- Most of the Staph strains are resistant.
- Not active against gram-negative (gm −ve) bacteria.
- Can be used for the treatment of enterococci infection with combination of aminoglycoside unless high resistance exists for aminoglycoside.
- All penicillins have a poor penetration to cerebral spinal fluid (CSF) except in the case of inflammation.
- Pen VK is used orally.
- Pen G benzathine is longer acting than Pen G procaine.

5.2.4 Aminopenicillins

- Amoxicillin and ampicillin
- Broader spectrum then PCN, cover some gm −ve bacteria including nonbeta-lactamase producing *Haemophilus influenza*, and enteric if susceptible.
- About 30% of *H. influenza* are resistant.
- Drug of choice for enterococci (*Enterococcus faecalis* and *Enterococcus faecium*) usually used with aminoglycoside for synergistic effect.
- Also cover Streptococcus species, listeria, actinomyces species, *B. burgdoferi, N. meningitidis, P. multicocida*, and peptostreptococci.
- Ampicillin and amoxicillin have same spectrum of activity except amoxicillin better absorb orally.

  Uses:
  - Enterococcal infection, urinary tract infection (UTI), sinusitis, upper respiratory infection (URI), otitis media, and listeria meningitis

5.2.5 Combination with beta-lactamase inhibitor

- Amoxicillin/Clavulanate (PO) and Ampicillin/Sulbactam (IV).
- Broad spectrum, cover beta-lactamase-producing organisms such as *H. influenza*, Moraxella, and anaerobes including *Bacteroides fragilis*.
- Also cover Strep and MSSA (methicillin-sensitive staph), and gram-negative bacteria.
- No coverage for pseudomonas.

  Uses:
  - Sinusitis, cellulitis, respiratory tract infection, otitis media, and sinusitis

5.2.6 Beta-lactamase resistance penicillin

- Dicloxacillin (PO), Methicillin, Nafcillin, and Oxacillin are IV
- Covers methicillin-sensitive *Staphylococcus aureus* (MSSA), *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, Staph coagulase negative, and Streptococcus species
- Methicillin-resistant *Staphylococcus aureus* (MRSA) are resistant
- Nafcillin has less cases of hepatitis and rash than oxacillin

  Uses:
  - Cellulitis, osteomyelitis, endocarditis, and bacteremia

5.2.7 Antipseudomonas penicillin

- Piperacillin and Ticarcillin
- Used with beta-lactamase inhibitors such as tazobactam
- Cover gram-positive, gram-negative, anaerobes, pseudomonas, and SPICS-A organisms.
- Synergistic effect with aminoglycoside for *Pseudomonas aeruginosa*
- Decrease in dosing is required in the case of renal impairment.

- Drug-induced immune thrombocytopenia and myelosuppression have been reported.
  Uses:
  - Hospital-acquired pneumonia
  - Cellulitis and soft tissue infection
  - Intra-abdominal infection

5.2.8 Cephalosporin

- Better staphylococcus coverage
- Cover gram-positive and some gram-negative bacteria
- No anaerobic coverage except Cefoxitin and Cefotetan
- No enterococci coverage except Ceftaroline
- No MRSA coverage except Ceftaroline
- Cephalosporin poorly penetrates ICF and vitreous humor
- Only Ceftriaxone, Cefotaxime, Ceftazidime, and Cefepime reach CSF in high enough concentration
- Ceftazidime, Cefoperazone, and Cefepime have antipseudomonas activity

Further divides into five generations based on the spectrum.

5.2.8.1 First generation

Cefadroxil, Cephalexin, Cephradine, and Cefazolin

- Only Cefazolin uses IV; all others are used orally.
- Mostly cover gram-positive cocci including MSSA and Strep.
  Uses:
  - Cefazolin is used for prophylaxis before surgery
  - Uncomplicated mild to moderate skin/soft tissue infections
  - Uncomplicated UTI

5.2.8.2 Second generation

- Cefaclor—PO
- Cefotetan—IV
- Cefoxitin—IV
- Cefprozil—PO
- Cefuroxime—PO/IV
- Loracarbef—PO
- Gram-positive coverage inferior then first generation, but better gram-negative coverage including *H. influenza*, enterobacteria, and Neisseria species.
- Cefoxitin and Cefotetan are active against Bacteroides including *B. fragilis*, but resistance is increasing.
  Uses:
  - Uncomplicated UTI, mild to moderate intraabdominal infection, diabetic foot infection, and respiratory infection

5.2.8.3 Third generation

Cefdinir—PO	**Cefditoren—PO**
Cefdinir—PO	Cefditoren—PO
Cefixime—PO	Cefoperazone—IV
Cefotaxime—IV	Cefpodoxime—PO
Ceftazidime—IV	Ceftibuten—PO
Ceftizoxime—IV	Ceftriaxone—IV

- Poor gm +ve activity as compared to first generation, but better then second generation.
- Cefixime and Ceftibuten have very weak Staph-aureus activity.
- Good gm −ve activity including *H. influenza, Escherichia coli, Klebsiella pneumonia*, Proteus, and Neisseria.
- No activity against ampC (cephalosporinase) or extended-spectrum beta-lactamase (ESBL) producing organism.
- Ceftazidime and Cefoperazone are antipseudomonas Cephalosporin.
- Ceftazidime has very weak gram-positive and anaerobic activity.
- Cefoperazone may cause disulfiram like reaction with alcohol due to the inhibition of aldehyde dehydrogenase.
- Ceftriaxone has the longest half-life in this group and has been associated with biliary pseudolithiasis.

  Uses:
  - Community-acquired pneumonia with azithromycin, meningitis, peritonitis, soft tissue infection, UTI, pyelonephritis, osteomyelitis, gonorrhea, and other infections

5.2.8.4 Fourth generation

Cefepime—IV

- Broad spectrum, cover gram-positive and gram-negative organism including pseudomonas.
- Gram-positive activity is similar to ceftriaxone or cefotaxime but has better gram-negative coverage.
- Poor anaerobic activity.

  Uses:
  - Hospital-acquired pneumonia, meningitis, complicated UTI, and several other infections

5.2.8.5 Fifth generation

Ceftaroline—IV

- Active against MRSA, VISA, VRSA, and strep.
- Gram-negative coverage is similar to third generation.
- No antipseudomonas activity.
- No coverage for ESBL-producing organism.

Uses:

- Skin and soft tissue infection (SSTI) and community-acquired pneumonia

5.2.8.6 Summary of cephalosporin (Table 5.1)

Table 5.1 Summary of cephalosporin.

Generation	Spectrum	Uses/Comments
First generation	Good Gm +ve coverage including MSSA, Strep group A. Few Gm −ve such as *E. coli*, Klebsiella, and *P. mirabilis*	Uncomplicated UTI, mild to moderate cellulitis or soft tissue infection
	Poor anaerobic spectrum	*Cefazolin. Prophylaxis before surgery
Second generation	Gm +ve cocci, better Gm −ve coverage including *H. influenza*, enterobacteria and Neisseria	Uncomplicated UTI
	Cefoxitin and cefotetan has anerobic coverage	Mild to moderate intraabdominal infection
Third generation	Gm +ve coverage. Ceftazidime has no Gm +ve activity. Excellent Gm −ve coverage. No pseudomonal activity, except Ceftazidime	CAP (ceftriaxone + azithromycin)
	No anaerobes	Meningitis, peritonitis, cellulitis, endocarditis, UTI, pyelonephritis, osteomyelitis, and gonorrhea
Fourth generation	Broad spectrum. Gm +ve including MSSA and Strep. Gm −ve coverage including Pseudomonas No activity against MRSA Weak activity against anaerobe	HAP, meningitis, and complicated UTI
Fifth generation	Active against MRSA, VISA, and VRSA No coverage for Pseudomonas and ESBL organism	SSTI and CAP

CAP, community-acquired pneumonia; *Gm +ve*, gram-positive bacteria; *Gm −ve*, gram-negative bacteria; *HAP*, hospital-acquired pneumonia; *MRSA*, methicillin-resistant Staph aureus; *SSTI*, skin and soft tissue infection; *VISA*, vancomycin intermediate Staph aureus; *VRSA*, vancomycin-resistant Staph aureus.

5.3 Carbapenems

Imipenem-cilastatin, Meropenem, Ertapenem, and Doripenem

- All are used as IVs.
- Imipenem used with dihydro-peptidase inhibitor cilastatin.

- Very broad spectrum, cover gram-positive, gram-negative including Pseudomonas, ESBL, SPICE, and anaerobe.
- No MRSA, VRE, and atypical coverage.
- Ertapenem has no antipseudomonas activity.
- Imipenem lower seizure threshold.

  Uses:
  - Hospital-acquired pneumonia (HAP), meningitis, complicated SSTI, and intraabdominal infection

5.4 Monobactam

5.4.1 Aztreonam

- Bind to penicillin-binding protein-3 (PBP-3) and inhibit cell wall synthesis.
- Only have gram-negative activity including pseudomonas, but resistance is increasing.
- No gram-positive and anaerobe coverage.
- No cross-sensitivity with PCN.

  Uses:
  - HAP, UTI, intraabdominal infections, and SSTI
  - Used in combination with other antibiotics

5.5 Lipoglycopeptide

5.5.1 Vancomycin and dalbavancin

- Used as IVs.
- Only have gram-positive coverage.
- Inhibit peptidoglycan by complexing D-alanine-D-alanine protein.
- Drug of choice for MRSA.
- For MSSA, Nafcillin is more effective than Vancomycin.
- Avoid using Vancomycin if MIC >2 for MRSA.
- Monitor trough or area under the curve (AUC) to decrease side effects such as nephrotoxicity and ototoxicity.
- Infuse slowly to avoid red man syndrome.
- Give diphenhydramine and acetaminophen if patient still has the infusing reaction.
- Oral Vancomycin does not absorb. Use orally for *Clostridium difficile* infection.
- Dalbavancin dose once a week.

  Uses:
  - Staph infection including MRSA, Strep, and non-VRE Enterococcus
  - Meningitis, bacteremia, PNA, and SSTI

5.6 Linezolid

- Available in both form, IV and oral
- Bacteriostatic
- Inhibit 50s ribosomal subunit
- Cover all gram-positive including MRSA, VRE, streptococcus sp.
- MAO inhibitor, avoid using with SSRI
- Bone marrow suppression and thrombocytopenia
- Long-term use may cause mitochondrial toxicity, peripheral neuropathy, optic neuritis, and blindness

  Uses:
  - Hospital-acquired pneumonia and SSTI
  - MRSA and VRE infection

5.7 Daptomycin

- Bactericidal, lipopeptide
- Binds to bacterial cell membrane and cause rapid depolarization resulting in the disruption of protein synthesis and cell death
- Only covers gram-positive bacteria including MRSA, VRE, strep, and Enterococcus
- Do not use for lung infection. Surfactant in the lungs deactivate it
- Poor CNS and bone penetration
- Myalgia, rhabdomyolysis, and peripheral neuropathy are common side effects
- Check CK and avoid statin

  Uses:
  - SSTI, MRSA, and VRE bacteremia and endocarditis
  - Resistance developed quickly if used long term

5.8 Inhibitor of protein synthesis in bacterial cell

5.8.1 50s ribosomal subunit inhibitors

5.8.1.1 Macrolide

- Includes Azithromycin, Clarithromycin, and Erythromycin
- Inhibits 50s subunit
- Covers some gram-positive and gram-negative bacteria
- First-line treatment for atypical infection
- Used in combination with ceftriaxone for CAP
- QT prolongation

  Uses:
  - STD (Chlamydia)
  - Sinusitis, bronchitis, walking PNA, CAP with ceftriaxone
  - Erythromycin is the drug of choice for Legionnaire disease

5.8.1.2 Clindamycin

- Bacteriostatic
- Inhibits 50s subunit
- Uses IV or PO
- Covers gram-positive cocci and anaerobe, including some MRSA (community acquired)
- It does not penetrate CSF

5.8.1.3 Chloramphenicol

- 50s ribosomal subunit inhibitor.
- Broad spectrum cover gram-positive including MRSA, gram-negative, and anaerobic bacteria including *B. fragilis*.
- Does not cover pseudomonas.
- Covers Coxiella, Ehrlichia, Rickettsia, Spirochetes typhoid, and Paratyphoid Salmonella.
- Bone marrow suppression is dose related and reversible.
- Rarely causes aplastic anemia that is irreversible.
- Gray baby syndrome in very young and premature babies.

  Uses:

  - Not commonly used in the United States of America because of some serious side effects.
  - Bacterial meningitis where the patient has PCN allergy.
  - Rocky Mountain fever in young children and pregnant women.

5.8.2 30s ribosomal subunit inhibitors

5.8.2.1 Tetracycline

- Tetracycline, Minocycline, and Doxycycline.
- 30s ribosomal inhibitors.
- Have limited gram-positive including MRSA and gram-negative coverage.
- Cover atypical bacteria such as anthrax, brucella, lyme disease, rickettsia, tularemia, and Q fever.
- Photosensitivity, teeth discoloration, stop bone growth in young children, GI problem, and hepatic toxicity.

  Uses:

  - Acne, SSTI, lyme disease, and Rocky Mountain spotted fever.

5.8.2.2 Aminoglycosides

- Amikacin, Gentamycin, Streptomycin and Tobramycin, and Neomycin
- All are used as IVs except Neomycin which is topical
- Bactericidal
- Inhibit 30s ribosomal subunit

- Cover gram-negative bacteria including pseudomonas
- No gram-positive or anaerobe coverage except staphylococcus
- Use synergistically with beta-lactam against Gm +ve organisms for endocarditis
- Poor CSF and urine penetration
- Neomycin is used only topically for skin infection. Too toxic for IV administration
- Nephrotoxicity reversible
- Ototoxicity irreversible
- Neuromuscular blockade→ prolong the effect of neuromuscular blockers

  Uses:
  - Gram-negative infection including pseudomonas
  - Used in combination with other antibiotics for HAP/ACAP/VAP

5.9 Metronidazole

- Active against anaerobic bacteria such as Bacteroides, Fusobacterium species, Clostridium species, *Helicobacter pylori*, Prevotella species, and *Trichomoniasis* vaginalis.
- Also affective against *Entamoeba histolytica* and *Giardia lamblia*.
- Inhibit protein synthesis by breaking helical DNA strand by forming nitroso-free radical which results in cell's death.

5.10 DNA gyrase and topoisomerase inhibitors

5.10.1 Fluoroquinolones (FQ)

- Ciprofloxacin, Delafloxacin, Levofloxacin, Moxifloxacin. Norfloxacin, Gatifloxacin, and Ofloxacin
- Available in PO and IVs and topical solution
- Bactericidal
- Inhibit enzyme DNA Gyrase and Topoisomerase IV
- Cipro has good gram-negative coverage but weak gram-positive and anaerobic coverage
- Levofloxacin has excellent coverage for *Strep pneumoniae*
- Cipro and levofloxacin have antipseudomonas activity
- Moxifloxacin has no antipseudomonas and no urine activity
- Moxifloxacin is the most active FQ against anaerobic
- Delafloxacin is less active against pseudomonas than ciprofloxacin
- Delafloxacin is the only FQ that has activity against MRSA, streptococci and staphylococci strains resistant to levofloxacin

Uses:
- Cipro is used for UTI, antipseudomonas in combination with other antibiotics and in bone infection, and proctitis.
- Levofloxacin is used for CAP, sinusitis, and bronchitis.
- Moxifloxacin is used for intraabdominal infection with metronidazole.

Norfloxacin (PO): Poorly absorbed spontaneously bacterial peritonitis.

5.11 Folic acid inhibitors

5.11.1 Sulfamethoxazole/trimethoprim (PO, IV)

- Bacteriostatic
- Sulfamethoxazole inhibits bacterial dihydrofolic acid by competing with para-aminobenzoic acid (PABA). Trimethoprim blocks enzyme dihydrofolate reductase (DHFR) which is required for the production of tetrahydrofolic acid
- Broad spectrum, cover most of gram-positive including community-acquired MRSA and gram-negative bacteria
- Doesn't cover pseudomonas
- Has activity against Listeria, Nocardia, *Pneumocystis jiroveci*, and *Toxoplasma gondii*
- PO form is almost 100% bioavailable
- May cause hypersensitivity reaction, bone marrow depression (dose dependent), false increase of creatinine level due to blockage of tubule creatinine secretion, hyperkalemia, methemoglobinemia, and hemolysis in patients with G6PD deficiency

  Uses:
  - CA-SSTI, PCP PNA, UTI, listeria infection, traveler's diarrhea, otitis media, bronchitis, and nocardiosis

5.12 Miscellaneous

5.12.1 Quinupristin/dalfopristin (IV)

- Streptogramin antibiotic
- Bacteriostatic
- Inhibits protein synthesis by acting on bacterial ribosome
- Active against staphylococcus and streptococcus species
- Covers MRSA and VRE
- Does not cover *E. faecalis*
- Causes thrombophlebitis. Uses central line for administration
- CYP450 inhibitor
- May cause myalgia and arthralgias

5.12.2 Tigecycline (IV)

- Bacteriostatic
- Glycylcycline → tetracycline analogs
- Binds to bacterial 30s ribosomal subunit and prevents the elongation of peptide chains
- Broad spectrum, covers gram-positive including MRSA and VRE, gram-negative including anaerobe and atypical
- FDA black box warning → increases the risk of death

Uses:

- SSTI and intraabdominal infections

5.13 Antibiotics for high resistance bacteria

Infection	Antibiotics	Comments
MRSA	Vancomycin	Drug of choice
	Linezolid	Bacteriostatic. Use other agents in endocarditis
	Daptomycin	Inactivated in lung. Do not use it for pneumonia. Poor CNS and bone penetration
	Synercid (Quinupristin/Dalpristin).	Thrombophlebitis. Require central line.
	Tigecycline	FDA black box warning→ ↑mortality
	Ceftaroline	
Vancomycin-resistant enterococci (VRE)	All above except vancomycin	
Enterococcus	Vancomycin	↑ resistance to vancomycin, ampicillin
	Ampicillin and Carbapenem	
	Levofloxacin	
	Piperacillin	
Extended-spectrum beta-lactamases (ESBL), *E. coli*, Klebsiella sp	Ceftolozane-tazobactam Ertapenem, Imipenem-cilastatin, Meropenem, Aminoglycoside	Resistant to Penicillin, Penicilin beta-lactamase inhibitor combination, and Aztreonam
Klebsiella pneumoniae Carbapenemase (KPC)	Ceftazidime-avibactam, Meropenem-vaborbactam, Imipenem-cilastatin-relabactam, Cefiderocol	Resistant to Penicillin, combination of Penicillin-BLI, Cephalosporin, Carbapenems Aztreonam BLI=beta-lactamase inhibitor

5.14 Antipseudomonal antibiotic

Antibiotics	Comments
Ceftazidime and Cefepime	
Carbapenem	Except Ertapenem
Aztreonam	High resistance
Piperacillin-tazobactam	High resistance to Ticarcillin
Fluoroquinolones	Except Moxifloxacin
Aminoglycoside	Used in combination with other antibiotics

5.15 Antibiotics for anaerobic bacteria

Antibiotics	Comments
Metronidazole	No activity against *Propionibacterium acnes*, Actinomyces and Lactobacillus, microaerophilic streptococci or gram-positive oral anaerobe.Excellent activity against Bacteroides, *E. histolytica*, and *G. lamblia*
Carbapenem	Excellent coverage
Cefoxitin and cefotetan	Bacteroides are increasingly resistant
Amoxicillin-clavulanate, piperacillin-tazobactam, ticarcillin-clavulanate	Preferably above the waist infection due to *E. coli* high resistance 40% or more Bacteroides are resistant. Above the diaphragm infection
Ampicillin-sulbactam	
Clindamycin	Bacteroides are increasingly resistance
Tigecycline	↑mortality rate
Moxifloxacin	
Chloramphenicol	May cause irreversible aplastic anemia

5.16 Bacterial resistance

Bacterial resistance can be classified into:

- Intrinsic
- Acquired

Intrinsic resistance: Inherent resistance, display by all members of the species, shared universally, and independent of previous exposure to antibiotics. For example, *Klebsiella pneumoniae* is resistant to ampicillin. Bacteroides are resistant to aminoglycoside and many beta-lactams, gram-positive bacteria are resistant to aztreonam, listeria monocytogenes are resistant to cephalosporin, and enterococci are resistant to

aminoglycoside, cephalosporin, and lincosamides. *E. coli* is resistant to macrolide, and all gram-negative bacteria are resistant to glycopeptides and lipopeptides.

Acquired resistance: This type of resistance is bacteria acquired through chromosomal gene mutation or from horizontal transfer of genes from plasmid or any other mechanism of gene transfer.

There are several general mechanisms via which bacteria become resistant to antibiotics:

- ↓the penetration of antibiotics to the active site: Gram-negative bacteria have an outer membrane that prevents beta-lactam to freely bind with a penicillin binding protein (PBP) site. Beta-lactams must pass through porins (protein channels) to reach the plasma membrane and bind to PBP. Mutation in these channels or a decrease in the number of porins present results in decreased access of antibiotics to the active site and results in antibiotic resistance. For example, *Neisseria gonorrheae* become resistant to beta-lactams and tetracycline by a mutation in porin channels. Enterobacteriaceae reduce the number of porin channels on its membrane to become resistant to carbapenems.
- Production of enzymes: There are several bacteria that produce various enzymes to inactivate the antibiotics. The most common one is beta-lactamase-producing bacteria. Beta-lactamase hydrolyzes the ring structure of beta-lactam, causing the ring to open and become ineffective. Many gram-negative bacteria produce beta-lactamase and are resistant to penicillin and cephalosporin. There are different types of beta-lactamase and can be classified into:
  - Based on molecular structure (amino-acid): Beta-lactamases are classified into four classes. A through D. Class A, C, and D hydrolyze the beta-lactam ring via serine residue at the active site of the beta-lactam ring, while class B (MBL = metallo-beta-lactamase) hydrolyze the ring using zinc to break the amide bond. This class is further discussed in Section 5.17.
  - Based on the functional group: Three groups: cephalosporinase, serine beta-lactamases, and MBLs (zinc-dependent).
  - Based on enzyme family: TEM (named after the first patient), SHV (sulfhydryl variable), CTX (hydrolyze cefotaxime), and OXA (hydrolyze Oxacillin).
  - AmpC gene was first isolated from *E. coli*. The gene produces AmpC beta-lactamases, which inactivate penicillin and the first generation of cephalosporin.
  - ESBL includes TEM, SHV, CTX, and OXA enzyme families.
  - Carbapenemases: Two types:
    - *Klebsiella pneumoniae* carbapenemases (KPCs): Belong to class A. Resistance to all beta-lactam but not to beta-lactamase inhibitors.
    - Carbapenem-resistant enterobacteriaceae (CRE): Belong to class B (MBLs). Resistance to all beta-lactam and are not inactivated by beta-lactamase inhibitors.

  - Non-beta-lactam beta-lactamase inhibitors: Avibactam and vaborbactam are developed to use with ceftolozane and meropenem. Effective against ESBL but not very effective against CRE.
- Efflux pumps: Most genes encode for efflux of drugs are chromosomally encoded. Many bacteria pump the drug out of the cell and lower the concentration. Various types of efflux pumps are expressed or induced under certain conditions such as the presence of drug molecules or other chemicals. Efflux pumps can be classified into five classes:
  - ATP-binding cassette (ABC). Use energy from ATP hydrolysis. It contains pumps that can transport drugs, amino acids, proteins, and several other molecules. This kind of pump is found in *Vibrio cholera* and is responsible for transporting fluoroquinolones and tetracycline out from bacterial cells.
  - Multidrug and toxic compound extrusion (MATE) pump: This family of pumps uses Na+ gradient as the energy source. This kind of pump is found in *Neisseria gonorrhea* and *Neisseria meningitides*. Mostly efflux fluoroquinolone and other molecules.
  - Small multidrug resistance (SMR) pumps: Use proton pump as a driving force to pump out ampicillin, erythromycin, and tetracycline. Found in *Staphylococcus epidermidis* and *E. coli*. *E. coli* pumps also transport vancomycin, erythromycin, and tetracycline out of the cell.
  - Major facilitator superfamily (MFS) pumps: Use symport and antiport pump system to transport out macrolides, tetracycline, fluoroquinolone, chloramphenicol, and trimethoprim. This kind of pump has been found in *Acinetobacter baumannii*, *E. coli*, and *S. aureus*.
  - Resistance-nodulation-cell division (RND) pumps: Found in many gram-negative bacteria, especially in *Pseudomonas aeruginosa*. It uses an antiport system to efflux several antibiotics such as beta-lactam, chloramphenicol, tetracycline, and fluoroquinolone.
- Alteration of the binding site: Some bacteria are able to change the binding site and making the antibiotics ineffective. Beta-lactam antibiotic binds to PBP. Some gram-positive bacteria such as *S. aureus* acquire mecA gene, which decreases the expression of PBPs or alters the site, resulting in lower affinity or totally inhibit the binding of the drug to PBPs. Resistance to vancomycin is acquired by acquiring van genes that change the peptidoglycan and decrease the binding affinity for vancomycin. Similarly, methylation of ribosomal subunits results in developing resistance to aminoglycoside, macrolides, and tetracycline. Alteration in DNA gyrase by acquiring gyraA or grlA gene results in resistance to fluoroquinolone.
- Inhibit the metabolic pathways: Mutation, which results in structural changes of the enzyme, alters the binding site and decreases the drug's ability to bind it. For example, DHFR in the metabolic pathway for folic acid metabolism is necessary for DNA synthesis. Structural changes in the enzyme would cause the inability of sulfonamide to bind the enzyme.

5.17 Resistance to beta-lactam

- Decrease penetration to the plasma membrane and decrease binding to active site
- Alteration in PBP
- Production of enzymes that cleave penicillin. Examples are penicillinases, cephalosporinases, and beta-lactamases
- Plasmid-mediated beta-lactamases are mostly produced by gram-negative bacteria and make first and second-generation cephalosporin inactive. While ESBLs rendered cephalosporin and aztreonam inactive
- Chromosomal-mediated beta-lactamases (AmpC) are produced by indole-positive Proteus, Serratia, Morganella sp., and Citrobacter and are resistant to all beta-lactams except Carbapenems
- Type of beta-lactamases:
  - There are various types of beta-lactamases. According to structural homology also called Ambler's classification, beta-lactamases are divided into four groups.
    - Group A: This group include:
      - ➢ penicillinases that hydrolyze narrow spectrum penicillin and early generation cephalosporin. Usually produced by staphylococcus sp. This enzyme can be blocked by clavulanate, sulbactam, and tazobactam
      - ➢ ESBLs hydrolyze most cephalosporin, monobactam, and extended-spectrum penicillin (piperacillin). Produced by some Klebsiella sp. *E. coli*, and other Enterobacteriaceae. Blocked by avibactam, relebactam, and vaborbactam
      - ➢ carbapenemases (serine) that hydrolyze carbapenems and all other beta-lactams. Secreted by some Enterobacteriaceae. Blocked by avibactam, relebactam, and vaborbactam
      - ➢ KPC (*Klebsiella pneumoniae* carbapenemases). Produced by Klebsiella sp. Blocked by avibactam, relebactam, and vaborbactam
    - Group B:
      - ➢ MBLs (metallo-beta-lactamases): Have active site consisting of metallic ions instead of serine as compared to other groups. Hydrolyze all beta-lactams except aztreonam. This enzyme is chromosomal coded and secreted by some species of *Stenotrophomonas maltophilia,* Klebsiella, Pseudomonas, and Acinetobacter. No blocking agent is available. However, aztreonam has limited activity
    - Group C:
      - ➢ AmpC or cephalosporinase hydrolyze cephalosporin and less extent to benzylpenicillin and monobactam
    - Group D:
      - ➢ Oxacillinase: Hydrolyze cloxacillin and oxacillin. Produced by some staphylococcus species. Blocked by avibactam

5.18 Antibacterial activity spectrum

Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
Penicillin G IV	***E. faecalis, Strep. agalactiae, Strep. anginosus gp. Strep gp C, F, G, Strep. pneumoniae, Strep. pyogenes, C. diphtheriae***, *Arcanobacter sp., L. monocytogenes*	***Leptospira sp., P. multocida, T. pallidum***, *B. burgdoferi, Kingella sp., N. meningitidis*	***Actinomyces sp., Clostridium sp., Peptostreptococci, P. acnes***
Pen VK PO	All of the above except *E. faecalis, L. monocytogenes*	Except Leptospira sp., *T. pallidum, B. burgdoferi*	***Actinomyces sp., Peptostreptococci, P. acne****, Clostridium sp.*
Amoxicillin PO	***E. faecalis***, *Arcanobactersp., C. diphtheriae, Strep. agalactiae, Strep. anginosus sp., Strep. gp. C, F, G, Strep. pneumoniae, Strep. pyogenes*	***B. burgdoferi, N. meningitidis, P. multocida***, *Leptospira sp., C. trachomatis, P. mirabilis*	***Actinomyces sp., Peptostreptococci***, *Clostridium sp., P. acnes*
Ampicillin IV, PO	***E. faecalis, L. monocytogenes***, *Arcanobactersp., C. diptheriae, Strep. agalactiae, Strep. anginosus gp., Strep. Gp. C, F, G, Strep. pneumoniae, Strep. pyogenes*	***B. burgdoferi, N. meningitidis, P. multocida***, *C. trachomatis, Kingella sp., Leptospira sp., P mirabilis*	***Actinomyces sp., Peptostreptococci***, *Clostridium sp., P. acnes*
Amox- clavulante PO	***S. saprophyticus***, *Arcanobactersp., C. diphtheriae, E. faecalis, L. monocytogenes, S. aureus (MSSA), S. epidermidis, S. lugdunensis, Staph. coag-negative, Strep. agalactiae, Strep. anginosus gp. Strep. Gp. C, F, G, Strep. pneumonia, Strep. pyogenes*	***Capnocytophaga, H. influenza, M. catarrhalis, P. multocida***, *B. burgdoferi, C. jejuni, E. coli, Eikenella sp., Kingella sp. klebsiella sp., Leptospira sp., P. mirabilis, P. vulgaris, Salmonella sp., Shigella sp.*	***B. fragilis***, *Actinomyces sp., Clostridium sp., P. acnes, Peptostreptococci, F. necrophorum*
Ampicillin-sulbactam IV	*S. saprophyticus, Arcanobactersp., C. diphtheriae, E. faecalis, L. monocytogenes, S. aureus (MSSA), S. epidermidis, S. lugdunensis, Staph. coag-negative, Strep. agalactiae, Strep. anginosus gp. ,Strep. gp C, F, G, Strep. pneumonia, Strep. Pyogenes*	***P. multocida, H. influenza***, *Capnocytophaga, B. burgdoferi, E. coli, Eikenella sp., Kingella sp., Klebsiella sp., Leptospira sp., P. mirabilis, P. vulgaris, Salmonella sp., Shigella sp.*	***B. fragilis***, *Actinomyces sp., Clostridium sp., P. acnes, Peptostreptococci, F. necrophorum*

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
Dicloxacillin	***S. aureus (MSSA), S. epidermidis, S. lugdune nsis, Staph.coagulase-negative***, *S. saprophyticus, Strep. Agalactiae, Strep. Anginosus, Strep. gp. C, F, G, Strep pneumoniae, Strep. pyogenes*	No coverage	No coverage
Nafcillin/Oxacillin IV	***S. aureus (MSSA), S. epidermidis, S. lugdune nsis, Staph.coagulase-negative***, *S. saprophyticus, Strep. agalactiae, Strep. anginosus, Strep. gp. C, F, G, Strep. pneumoniae, Strep. pyogenes*	No coverage	No coverage
Piperacillin-tazobactam	*Arcanobactersp., C. diphtheriae, E. faecalis, L. monocytogenes, S. aureus (MSSA), S. lugdunensis, S. saprophyticus Staph. coag-neg., Strep. agalactiae, Strep. anginosus, Strep. gp. C, F, G, Strep. pneumoniae, Strep. pyogenes*	***C. koseri, Capnocytophaga sp., E. coli, Klebsiella sp., M. morganii, P. aeruginosa***, *Eikenella sp., H. influenza, Kingella sp., Leptospira sp., M. catarrhalis, N. meningitidis, P. mirabilis, P. multocida, P. vulgaris, Providencia sp., Salmonella sp., Serratia sp., Shigella sp., Y. enterocolitica*	***B. fragilis***, *Actinomyces sp., Clostridium sp., P. acnes, Preptostreptococci, F. necrophorum*
Cephalosporin			
First-generation Cefazolin IV	***S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg.***, *Arcanobactersp., Strep. agalactiae, Strep. anginosus, Strep. gp. C, F, G, Strep. pneumonia, Strep. p yogenes, Viridans gp.*	*E. coli, Kingella sp., Klebsiella sp., P. mirabilis*	*P. acnes, Peptostreptococci*
Cefadroxil, Cephalexin, Cephradine	***S. saprophyticus***, *S. aureus (MSSA), S. epidermidis, S. lugdunensis, Staph. coag-negative, Strep. agalactiae, Strep. anginosus gp., Strep. group C, F, G, Strep. pneumoniae, Strep. p yogenes, Viridans group*	*P. mirabilis*	*P. acnes*

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
Second-generation Cefuroxime PO	*Arcanobactersp., S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg, Strep. agalactiae, Strep. anginosus gp., Strep. gp. C, F, G, Strep. pneumoniae, Strep. pyogenes, Strep. viridan gp.*	***B. burgdoferi***, *E. coli, H. influenza, Klebsiella sp., M. catarrhalis, P. mirabilis, P. multocida*	*P. acnes Peptostreptococci*
Cefaclor PO	***S. saprophyticus***, *Arcanobactersp., S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg, Strep. agalactiae, Strep. anginosus gp., Strep. gp. C, F, G, Strep. pneumoniae, Strep. pyogenes, Strep. viridan gp.*	*P. mirabilis*	*Peptostreptococci*
CefprozilPO	Same as cefuroxime	Same as cefuroxime except not active against *B. burgdoferi*	Same as cefuroxime
Cefuroxime IV	Same as PO Cefuroxime	Same as PO Cefuroxime plus *N. meningitidis*	Same as PO Cefuroxime
Cefoxitin/cefotetan IV	*Arcanobactersp., S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg, Strep. agalactiae, Strep. anginosus gp., Strep. gp. C, F, G, Strep. pneumoniae, Strep. pyogenes, Strep. viridans gp.*	*E. coli (ESBL), E. coli, Eikenella sp., H. influenza, K. granulomatis, Kingella sp., Klebsiella sp., M. morganii, P. mirabilis, P. vulgaris, Providencia sp.*	*Actinomyces sp., Clostridium sp., P. acnes, Peptostreptococci, Prevotella sp., F. necrophorum*
Third-generation Cefdinir PO Cefixime PO Cefpodoxime PO	*Arcanobactersp., S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg., Strep. agalactiae, Strep. anginosus gp., Strep. gp. C, F, G, Strep. pneumonia, Strep. pyogenes, Strep. viridans gp.*	*C. koseri, E. coli, H. influenza, Kingella sp., Klebsiella sp., M. catarrhalis, P. mirabilis, P. multocida, Salmonella sp., Shigella sp.* *Y. eneterocolitica* → Cefixime	No coverage Peptostreptococci → Cefixime
Cefotaxime IV	***Viridans gp***., *Arcanobactersp., S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg, Strep agalactiae, Strep. anginosus gp, Strep. gp. C, F, G, Strep pneumoniae, Strep. pyogenes*	***H. influenza, Leptospira sp., Y. enterocolitica***, *Aeromonas sp., B. burgdofer, C. koseri, Capnocytophaga sp., E. coli, Eikenella sp, Kingella sp., Klebsiella sp., M. catarrhalis, M. morgani, N. meningitidis, P. mirabilis, P. multocida, P. vulgaris, Providencia sp., Salmonella sp., Serratia sp., Shigella sp., V. parahemolyticus, V. vulnificus*	*Actinomyces sp., Clostridium sp., P. acnes, Peptostreptococci, F. necrophorum*

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
Ceftriaxone IV	***Viridans gp.***, *Arcanobactersp., S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg, Strep agalactiae, Strep. anginosus gp., Strep. gp. C, F, G, Strep. pneumoniae, Strep. pyogenes*	***B. burgdoferi, E. coli, H. ducreyi, H. influenzae, Kingella sp., Klebsiella sp., Leptospira sp., M. morganii, N. meningitidis, Y. enterocolitica***, *Aeromonas sp., C. koseri, Capnocytophaga sp., Eikenella sp., K. granulomatis, M. catarrhalis, P. mirabillis, P. multocida, P. vulgaris, Providencia sp., Salmonella sp., Serratia sp., Shigella sp., V. parahemolyticus, V. vulnificus*	Same as above
Ceftizoxime IV	Same as above but second line	Same as above but second line	Same as above but second line
Ceftazidime IV	No staph coverage, no Viridans gp. Rest is same as ceftriaxone.	***P. aeruginosa***, *Aeromonas sp., C. koseri, Capocytophagasp., E. coli (s), H. influenzae, Kingella sp., Klebsiella sp (s), M. catarrhalis, M. morganii, N. meningitidis, P. mirabilis, P. vulgaris, Providencia sp., Salmonella sp., Serratia sp., Shigella sp., V. parahemolyticus, V. vulnificus*	*P. acnes, Peptostreptococci*
Fourth-generation Cefepime IV	*S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg., Strep. agalactiae, Strep. anginosus, Strep. gp. C, F, G, Strep. pneumoniae, Strep. p yogenes, Viridans gp.*	***C. freundi, C. koseri, P. aeruginosa, Y. enterocolitic a***, *Aeromonas, Capnocytophaga sp., E. cloacae, E. coli, H. influenza, Kingella sp., Klebsiella sp., Leptospira sp., M. catarrhalis, M. morganii, N. meningitidis, P. mirabilis, P. multocida, P. vulgari s, Providenci a, Salmonell a, Serrati a, Shigella, V. parahemolyticus, V. vulnificus*	*P. acnes, Peptostreptococci*
Fifth-generation Ceftaroline	*Arcanobactersp., S. aureus (MRSA), S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg, Staph. agalactiae, Staph. anginosus, Strep. gp. C, F, G, Strep. pneumoniae, Strep. pyogenes, Viridian gp.*	*C. koseri, E. coli, H. influenza, Kingella sp., Klebsiella sp., M. catarrhalis, M. morganii, P. mirabilis, P. multocida*	*P. acnes, Peptostreptococci*

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
Ceftobiprole. Not approved in USA	Same as Ceftaroline		
Ceftolozane-tazobactam (Zerbaxa)	*Strep. agalactiae, Strep. anginosus gp., Strep. gp. C, F, G, Strep. pneumoniae, Strep. pyogenes, Viridans gp.*	***P. aeruginosa***, *C. freundii, C. koseri, E. cloacae, E. coli (ESBL), E. coli (S), H. influenza, Kingella sp., Klebsiella sp. (ESBL, S), M catarrhalis, P. morganii, P. mirabilis, P. multocida, P. vulgaris, Providencia sp., Serratia sp.*	*B. fragilis, P. acnes, Peptostreptococci, Prevotella*
Ceftazidime-avibactam	Same as ceftazidime plus activity→	Against ESBL, AmpC, and carbapenemase producing bacteria plus same as Ceftazidime.	*P. acnes, Peptostreptococci*
Cefiderocol↑all causes of mortality. In randomized trials, reserved for limited or no alternative treatment	No activity	Activity against ESBL, AmpC, Carbepenemase-producing gram-negative bacteria plus *A. baumannii, B. cepacian, C. freundi, C. koseri, E. cloaceae, E. coli* (ESBL, KPC, MBL, S), Klebsiella sp. (ESBL, KPC, MBL, S), *M. morganii, P. aeruginosa, P. mieabilis, P. vulgaris, S. maltophilia, Serratia sp.*	No activity
Carbapenems			
Doripenem IV	*Arcanobactersp., S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus*	***Providencia sp.***, *C. freundi, C. jejuni, C. koseri, Capnocytophaga sp., E. cloacae, E. coli (ESBL, S), Eikenella sp., H. influenza, Kingella sp., Klebsiella sp. (ESBL, S), Leptospira sp., M. catarrhalis, M. morganii, N. meningitidis, P. aeruginosa, P. mirabilis, P. multocida, P. vulgaris, Salmonella sp.*	*Actinomyces sp., B. fragilis, Clostridium sp., P. acnes, Peptostreptococci, Prevotella sp., F. necrophorum*
Ertapenem	*Arcanobactersp., S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg., Strep. agalactiae, Strep. anginosus gp., Strep. Gp. C, F, G., Strep. pneumoniae, Strep. pyogenes, Viridans gp.*	***E. coli (ESBL), Providencia sp.***, *Aeromonas sp., C. freundi, C. jejuni, C. koseri, E. cloacae, E. coli (s), Eikenella sp., H. influenza, Kingella sp., Klebsiella sp. (ESBL, S), Leptospira sp., M. catarrhalis, M. morganii, N. meningitidis, P. mirabilis, P. multocoida, P. vulgaris, Salmonella sp., Serratia sp., Shigella sp.*	***B. fragilis***, *Actinomyces sp., Clostridium sp., P. acnes, Peptostreptococci, Prevotella sp., F. necrophorum*

Continued

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
Imipenem-cilastatin IV	***Nocardia sp.***, *Arcanobactersp., E. faecalis, S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg gp., Strep. agalactiae, Strep. anginosus gp., Strep gp C, F, G, Strep pneumoniae, Viridans gp., Y. enterocolitica*	***E. coli (ESBL), Klebsiella sp. (ESBL)***, *Aeromonas sp., C. freundi, C. jejuni, C. koseri, Capnocytophaga sp., E. cloacae, E. coli (S), Eikenella sp., H. influenza, Kingella sp., Klebsiella sp (S)., Leptospira sp., M. catarrhalis, N. meningitidis, P. aeruginosa, P. multo cida, Salmon ella, Serratia, Shigella sp.*	***B. fragilis***, *Actinomyces sp., Clostridium sp., P. acnes, Peptostreptococci, Prevotella, F. necrophorum*
Meropenem IV, IM	*Arcanobactersp., S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg, Strep. agalactiae, Strep. anginosus gp., Strep. gp. C, F, G, Strep. pneumoniae, Strep pyogenes, Viridans gp.*	***C. freundii, C. koseri, E. coli (ESBL), P. aeruginosa, Providencia sp.***, *Aeromonas sp., C. je juni, Capnocytophaga, E. cloacae, E. coli (S), Eikenella sp., H. influenza, Kingella sp., Klebsiella sp., Leptospira sp., M. catarrhalis, M. morganii, N. meningitidis, P. mirabilis, P. multocida, P. vulgaris, Salmonella sp., Serratia sp., Shigella sp., Y. enterocolitica*	***B. fragilis***, *Actinomyces sp., Clostridium sp., P. acnes, Pepetostreptococci, Prevotella sp., F. necrophorum*
Meropenem-vaborbactam IV	Same as meropenem	Same as meropenem. Can also be used against beta-lactamases and serine carbapenemases producing bacteria	Same as meropenem
Monobactam			
Aztreonam IV	No activity	*Aeromonas, E. coli, H. influenzae, Klebsiella sp., Leptospira sp., M. catarrhalis, M. morganii, N. meningitidis, P. aeruginosa, P. mirabilis, P. multocida, P. vulgaris, Providencia, Salmonella sp., Serratia sp., Shigella sp., Y. enterocolitica*	No activity

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
Lipoglycopeptide			
Vancomycin IV	***Arcanobactersp., C. jeikeium, E. faecalis, S. aureus (MRSA), S. epidermidis (MRSE), Staph. coag-neg(R), Viridans gp.***, *S. aureus (MSSA), S. epidermidis (S), S. lugdunensis, S. saprophyticus, Staph. coag-neg (s), Strep. agalactiae, Strep. anginosus, Strep. gp. C, F, G, Strep. pneumoniae, Strep pyogenes, Viridans gp.*	No activity	*Clostridium sp., P. acnes, Peptostreptococci*
Dalbavancin. Long-acting use once a week. IV	Same spectrum as vancomycin but second-line treatment	No activity	Same as above but second-line treatment
Telavancin: use q24h IV	Same spectrum as vancomycin but second-line treatment	No activity	Same as vancomycin but second-line treatment
Teicoplanin: not available in USA	Same spectrum as vancomycin	No activity	Same spectrum as vancomycin
Oritavancin	*E. faecalis (VRE, S), E. faecium (VRE, S), S. aureus (MRSA, MSSA), S. epidermidis (R, S), S. lugdunensis, Staph. coag-neg gp., Strep. agalactiae, Strep. anginosus, Strep. gp. C, F, G, Strep. pyoenes, Viridan gp.*	No activity	*Clostridium sp., P. acnes, Peptostreptococci*
Daptomycin IV	***S. aureus (MRSA), S. epidermidis (R), Staph. coag-neg (R)***, *Arcanobactersp., C. jeikeium, E. faecalis (VRE, S), E. faecium (VRE, S), S. aureus (MSSA), S. epidermidis (S), S. lugdunensis, S. saprophyticus, Staph. coag-neg (S), Strep. agalactiae, Strep. C, F, G, Strep. pyogenes*	No activity	*P. acnes, Peptostreptococci*
Macrolides			
Azithromycin PO, IV	***Arcanobacter sp.***, *C. diphtheriae*	***B. pertussis, Bartonella sp., C. jejuni, C. trachomatis, H. ducrey, K. granulomatis, Legionella sp., Leptospira sp.***, *B. burgdoferi, C. burnetiid, H. influenzae, M. catarrhalis, P. multocida, S. lugdunensis, Salmonella sp., V. cholera, V. parahemolyticus*	*Actinomyces, Clostridium sp.*
Clarithromycin PO	***Arcanobacter sp***, *C. diphtheriae*	***B. pertussis, Bartonella sp., Legionella sp.***, *B. burgdoferi, C. burnetiid, C. jejuni, C. trachomatis, Chlamydophila sp., H. influenzae, K. granulomatis, Leptospira sp., M. catarrhalis, S. lugdunensis*	*Actinomyces sp., Clostridium sp.*

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
Erythromycin PO, IV	***Arcanobacter sp.,*** ***C. diphtheriae***, *S. lugdnensis*	***C. jejuni, H. ducreyi, K. granulomatis, Legionella sp.***, *B. burgdoferi, B. pertussis, Bartonella sp., C. burnetti, C. trachomatis, Chlamydophila sp., Leptospira, M. catarrhalis, V. cholera*	*Actinomyces sp., Clostridumsp.*
Fidaxomicin PO	No activity	No activity	***C. difficile***
30s ribosomal subunit inhibitor			
Tetracycline	*Arcanobactersp., S. aureus (MSSA), S. epidermidis (S), S. lugdunensis, S. saprophyticus, Staph. coag-neg (s)*	***M. pneumonia***, *B. burgdoferi, Bartonella sp., Brucella sp., C. burnetti, C. trachomatis, Capnocytophaga sp., Ehrilichiasp., Eikenella sp., F. necrophorum, F. tularensis, H. influenzae, K. granulomatis, Kingella sp., Legionella sp., Leptospira sp., M. catarrhalis, P. multocida, R. rickettsii, V. cholera, V. parahemolyticus, V. vulnificus, Y. pestis*	*Actinomyces sp., Clostridumsp., P. acnes,* Pe*ptostreptococci, Prevotella sp.*
Doxycycline	***Arcanobactersp.***, *Aeromonas, S. aureus (MSSA, MRSA), S. epidermidis (S), S. lugdunensis, S. maltophilia, S. saprophyticus, Staph. coag-neg. Gp.*	***B. burgdoferi, Bartonella sp., C. burnetti, C. trachomatis,*** Chlamydophila ***sp., Ehrlichia sp., F. tularensis, K. granulomatis, Leptospira sp., M. pneumoniae, R. rickettsii***, *Brucella sp., Capnocytophaga sp., Eikenella sp., F. necrophorum, H. influenzae, Kingella sp., Legionella sp., M. catarrhalis, P. multocida, V. cholera, V. parahemolyticus, V. vulnificus, Y. enterocolitica, Y. pestis*	*Actinomyces sp., Clostridumsp., P. acnes, Peptostreptococci, Prevotella sp.*
Minocycline	*Arcanobactersp., S. aureus (MRSA, MSSA), S. epidermidis (s), S. lugdunensis, S. maltophilia, S. saprophyticus, Staph. coag. Neg (S)*	***M. pneumoniae***, *Aeromonas sp., B. burgdoferi, Bartonella sp., Brucella sp., C. burnetiid, C. trachomatis, Capnocytophaga sp., Chlamydophila sp., Ehrlichia sp., Eikenella sp., F. necrophorum, F. tularensis,*	*Actinomyces sp., Clostridumsp., P. acnes, Peptostreptococci, Prevotella sp.*

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
		H. influenzae, K. granulomatis, Kingella sp., Legionella sp., Leptospira sp., M. catarrhalis, P. multocida. R. rickettsii, V. cholera, V. vulnificus, Y. pestis	
Fluoroquinolone			
Ciprofloxacin	*Arcanobactersp., S. saprophyticus*	***F. tularensis, H. ducrey, K. granulomatis, Legionella sp., Shigella sp., Y. enterocolitica***, *Aeromonas sp., Brucella sp., C. burnetiid, C. freundii, C. jejuni, C. koseri, Chlamydophiliasp., E. cloacae, E. coli (S), Eikenella sp., H. influenzae, Kingella sp., Klebsiellssp., Leptospira sp., M. catarrhalis, M. morganii, M. pneumoniae, P. aeruginosa, P. mirabilis, P. multocida, P. vulgaris, Providencia sp., Salmonella sp., Serratia sp., V. cholera, V. parahemolyticus, V. vulnificus, Y. pestis*	No activity
Levofloxacin	*E. faecalis (S), S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg (s), Strep. pneumoniae, Viridans gp.*	***C. trachomatis, H. influenzae, Kingella sp., Legionella sp., M. pneumoniae, Shigella sp., Y. enterocolitica***, *Aeromonas sp., C. burnetiid, C. freundii, C. jejuni, C. Koseri, Chlamydophila sp., E. cloacae, E. coli (S), Eikenella sp., H. ducreyi, Klebsiella sp., L. monocytogenes, Leptospira sp., M. catarrhalis, M. morgani, P. aeruginosa, P. mirabilis, P. multocida, P. vulgaris, Providencia sp., Salmonella sp., Serratia sp., V. parahemolyticus, V. vulnificus*	*Peptostreptococci*
Moxifloxacin	*S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg (S), Strep. Pne umoniae, Viridans gp.*	***H. influenzae, Legionella sp., M. pneumoniae,*** *Aeromonas sp., C. burnetiid, C. freundii, C. jejuni, C. koseri, C. trachomatis, Chlamydophila sp., E. cloacae, Klebsiella sp., L. monocytogenes, Leptospira sp., M. catarrhalis, P.*	*Peptostreptococci, Prevotella sp.*

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
		mirabilis, P. multocida, P. vulgaris, Providencia sp., Salmonella sp., Serratia sp., Shigella sp., Y. enterocolitica	
Delafloxacin	*E. faecalis, S. aureus (MRSA, MSSA), S. epidermidis (R, S), S. lugdunensis, S. saprophyticus, Staph. coag-neg (R, S), Strep. Agalactiae, Strep. Anginosus, Strep. gp. C, F, G, Strep pneumoniae, Strep. Pyogenes, Viridans gp.*	*Aeromoans sp., C. freundii, C. jejuni, C. koseri, E. cloacae, E. coli (S), H. influenzae, Kingella sp., Klebsiella sp., L. moncytogenes, Legionella sp., Leptospira sp., M. catarrhalis, M. morganii, P. aeruginosa, P. mirabilis, P. multocida, P. vulgaris, Provedenciasp., Salmonella sp., Serratia sp., Shigella sp., Y. enterocolitica*	*B. fragilis, Clostridium sp., Peptostreptococci*
Norfloxacin	*E. faecalis (S)*	*C. freundii, C. koseri, E. cloasae, E. coli (S), Klebsiellssp., M. morganii, P. mirabilis, P. vulgari s, Providencia gp.*	No activity
Gatifloxacin. Only as eye drop available in the USA	*Arcanobactersp., S. aureus (MSSA), S. epidermidis, S. lugdunensis, S, saprophyticus, Staph. coag-neg (S), Strep. pneumoniae, Viridans gp.*	*Aeromonas sp., C. burnetiid, C. freundii, C. jejuni, C. koseri, C. trachomatis, Chlamydophila sp., E. cloacae, E. coli (S), Klebsiella sp., L. monocytogenes, Legionellasp., Leptospira sp., M. catarrhalis, M. pneumoniae, P. mirabilis, P. multocida, P. vulgaris, Salmonella sp., Serratia sp., Shigella sp., Y. enterocolitica*	*Peptostreptococci*
Gemifloxacin. Not available in the US	*Arcanobactersp., E. faecalis (S), S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg (S), Strep pneumoniae, Viridans gp.*	*Aeromonas sp., C. burnetiid, C. freundii, C. jejuni, C. koseri, C. trachomatis, Chlamydophila sp., E. cloacae, E. coli (s), H. influenzae, Klebsiella sp., L. monocytogenes, Legionella sp., Leptospira sp., M. catarrhalis, M. pneumoniae, P. mirabilis, P. mulyocida, P. vulgaris, Salmonella sp., Serratia sp., Shigella sp.*	No activity
Ofloxacin	*S. lugdunensis, S. saprophyticus*	***C. trachomatis, Legionella sp.**, Aeromonas sp., C. burnetiid, C. freundii, C. jejuni, C. koseri, Chlamydophila sp., E. cloacae, E. coli (S), Eikenella sp., H. influenzae, Kingella sp., Klebsiella sp., Leptospira sp., M.*	No activity

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
		catarrhalis, M. morganii, M. pneumoniae, P. mirabilis, P. multocida, P. vulgaris, Providencia sp., Salmonella sp., Serratia sp., Shigella sp., V. ofloxacin parahemolyticus, V. vulnificus, Y. enteroclitica	
Aminoglycoside			
Amikacin	**Nocardia sp.**	*Aeromonas sp., C. freundi, C. jejuni, C. koseri, E. cloacae, E. coli (S), Klebsiella sp., M. morganii, P. aeruginosa, P. mirabilis, P. vulgaris, Providencia sp., Salmonella sp., Serratia sp., Shigella sp., Y. enterocolitica*	No activity
Gentamicin	No activity	***Bartonella sp., F. tularensis, Y. pestis***, *Aeromonas, Brucella sp., C. freundii, C. jejuni, C. koseri, E. cloacae, E. coli (S), K. granulomatis, Kingella sp., Klebsiella sp., M. morganii, P. aeruginosa, P. mirabilis, P. vulgaris, Salmonella sp., Serratia sp., Shigella sp., Y. enterocolitica*	No activity
Kanamycin	No activity	*Mycobacterium tuberculosis*	No activity
Paromomycin	No activity	No activity against gram-negative bacteria but is used to treat the infection due to *Entamoaeba histolytica, Dientamoeba fragilis, Giardia intestinalis, amebas, and Visceral leishmaniasis*	No activity
Plazomicin	No activity	*E. coli (ESBL, KPC, MBL), Klebsiella sp. (ESBL, KPC, MBL), Serratia sp.*	No activity
Streptomycin	Viridans gp., Enterococci	*M. tuberculosis*	No activity
Tobramycin	No activity	*Aeromonas, C. freundii, C. jejuni, C. koseri, E. cloacae, E. coli (S), F. tularensis, Klebsiella sp. (S), M. morganii, P. aeruginosa, P. mirabilis, P. vulgaris, Salmonella sp., Serratia sp., Shigella sp., Y. enterocolitica*	No activity

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
Folate inhibitors			
Trimethoprim-sulfamethoxazole	***Nocardia sp.***, *S. aureus (MRSA, MSSA), S. epidermidis R, S), S. lugdunensis, S. saprophyticus, Staph. coag-neg (R, S), L. monocytogenes*	***K. granulomatis, S. maltophilia***, *Aeromonas, B. cepacian, B. pertussis, Brucella sp., C. burnetiid, E. cloacae, H. influenzae, Kingella sp., Klebsiella aerogenes, Legionella sp., M. catarrhalis, P. multocida, Serratia sp., Y. enterocolitica, Y. pestis*	No activity
Miscellaneous agents			
Metronidazole	No activity	*Entamoeba histolytica, Giardia lamblia, Trichomonas vaginalis*	***B. fragilis, Prevotella sp., F. necrophorum***
Chloramphenicol	*S. aureus (MSSA), S. epidermidis (R, S), S. Lugdunensis, S. maltophilia, S. saprophyticus, Staph. coag-neg (R, S), Strep. agalactiae, Strep. anginosus, Strep gp C, F, G, Strep. pneumoniae, Strep. p yogenes, Viridans gp.*	*Aeromonas sp., Brucella sp., C. burnetiid, Capnocytophaga sp., Chlamydophila sp., E. coli (S), Eikenella sp., F. tularensis, H. influenzae, K. granulomatis, Kingella sp., Klebsiella sp., Leptospira sp., N. meningitidis, R. rickettsii, Salmonella sp., Shigella sp., V. parahemolyticus, V. vulnificus, Y. pestis*	*Actinomyces, B. fragilis, Clostridumsp., F. necrophorum, Peptostreptococci, Prevotella sp.*
Fosfomycin	No activity	*C. freundii, C. koseri, E. coli (ESBL, S), H. influenzae, Klebsiella sp. (ESBL, S), P. mirabilis, Providencia sp.*	*Peptostreptococci*
Tigecycline	*Arcanobactersp., E. faecalis, E. faecium, S. aureus (MRSA, MSSA), S. epidermidis (R, S), S. lugdunensis, S. maltophilia, S. saprophyticus, Staph. Coag-neg (R, S), Strep. agalactiae, Strep. anginosus, Strep. gp. C, F, G, Strep. pneumoniae, Strep. pyogenes, Viridans gp.*	*Aeromoas sp., C. freundii, C. jeikeium, C. koseri. E. cloacae, E. coli (ESBL, KPC, MBL, S), H. influenzae, Kingella sp., Klebsiella sp. (ESBL, KPC, MBL, S), Legionella sp., M. pneumoniae, P. multocida, Salmonella sp., Serratia sp., Shigella sp.*	*B. fragilis, Chlamydophila sp., Clotridumsp., F. necorophorum, P. acnes, Peptostreptococci, Prevoltella sp.*
Clindamycin	***Arcanobactersp.***, *C. diptheriae, S. aureus (MSSA), S. epidermidis, S. lugdunensis, S. saprophyticus, Staph. coag-neg (S), Strep. agalactiae, Strep. anginosus gp., Strep gp. C, F, G, Strep. pneumonia, Strep. pyogenes*	**Capnocytophaga sp.**	***Actinomyces sp.***, *Clostridium sp., F. necorophonum, Peptostreptococci, Prevolta sp.*

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Antibacterial agents	Gram positive	Gram negative/no cell wall/ spirochete/parasite	Anaerobic
Linzolid	***E. faecalis (VRE), E. faecium (VRE, S), S. aureus (MRSA), S. epidermidis* (R), *Staph. coag-neg (R)***, *Arcanobactersp., E. faecalis (S), L. moncytogenes, S. aureus (S), S. epidermidis, S. lugdunensis, Staph. coag-neg (S), Strep. agalactiae, Strep. anginosisgp., Strep gp. C, F, G, Strep. pneumonia, Strep. pyog enes, Viridans gp., Nocardia sp.*	No activity	*Actinomyces, Clostridium sp., P. acnes, Peptostreptococci*
Lefamulin	*S. aureus (MRSA, MSSA), S. epidermidis (S), Staph. coag-neg (S), Strep. agalactiae, Strep. anginosus gp., Strep. pneumoniae, Strep. pyogene s, Viridans gp.*	*Chlamydophila sp., H. influenza, Legionella sp., M. catarrhalis, M. pneumoniae*	No activity
Quinupristin-Dalfopristin	*Arcanobactersp., E. faecium (VRE, S), S. aureus (MRSA, MSSA), S. epidermidis (R, S), S. lugdunensis, Staph. coag-neg (R, S), Strep. agalactiae, Strep. anginosus gp., Strep. Gp. C, F, G, Strep. pneumoniae, Strep. pyogenes, Viridans gp.*	No activity	No activity
Retapamulin (topical)	*S. aureus, Strep. pyogenes*	No activity	No activity

BOLD LETTERS → first-line therapy (sensitivity ++) REGULAR LETTERS → second-line therapy, (sensitivity +) R = methicillin resistant. *ESBL*, extended-spectrum beta-lactamase producer; *MRSA*, methicillin-resistant Staphylococcus; *MSSA*, methicillin-sensitive Staphylococcus; *S*, methicillin susceptible; *VRE*, vancomycin-resistant enterococci.

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6 Viruses

6.1 Description

Viruses are considered nonliving (when outside a cell) genetic material, which are surrounded by the protein coat called capsid. In some viruses, capsids are surrounded by lipid bilayers membrane derived from the host cell membrane and are called envelope. Some viruses have spikes like glycoproteins molecules on their out membrane, which have various functions, including attachment with the host cells receptors.

6.2 Classification

Viruses are classified in various ways:

a) Genetic material:
- RNA viruses
- DNA viruses

b) Capsids:
- Icosahedral
- Helical
- Complex

c) Envelope:
- Naked
- Enveloped

d) Size:

Average size 20–200 nm (Fig. 6.1)

6.2.1 RNA viruses

These viruses carry RNA as genetic material and are classified into single-stranded or double-stranded. Most RNA viruses are single-stranded except rotavirus, which is double-stranded. RNA strands are further classified into positive and negative strands. Positive strands can use their genome directly as mRNA and translate it into viral protein

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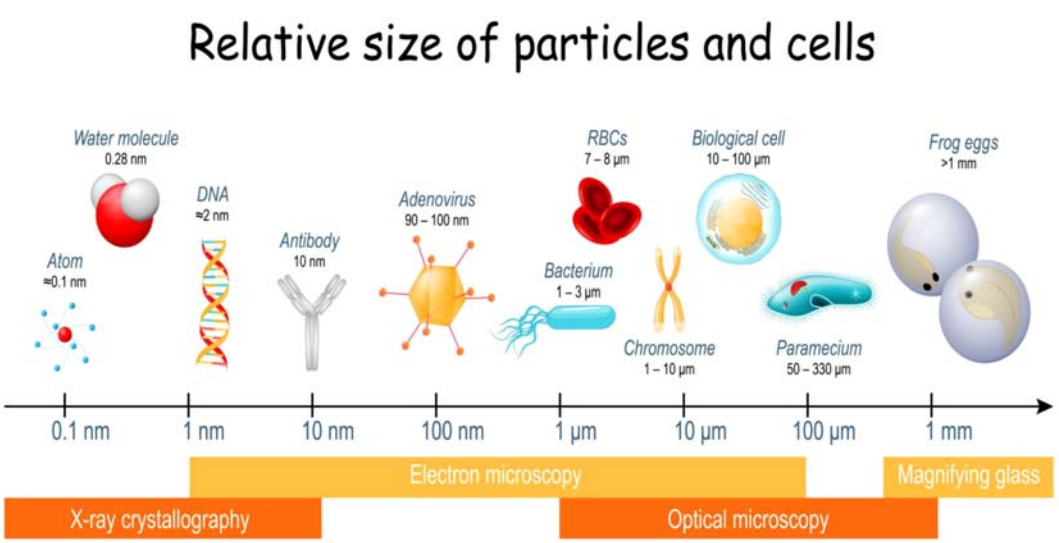
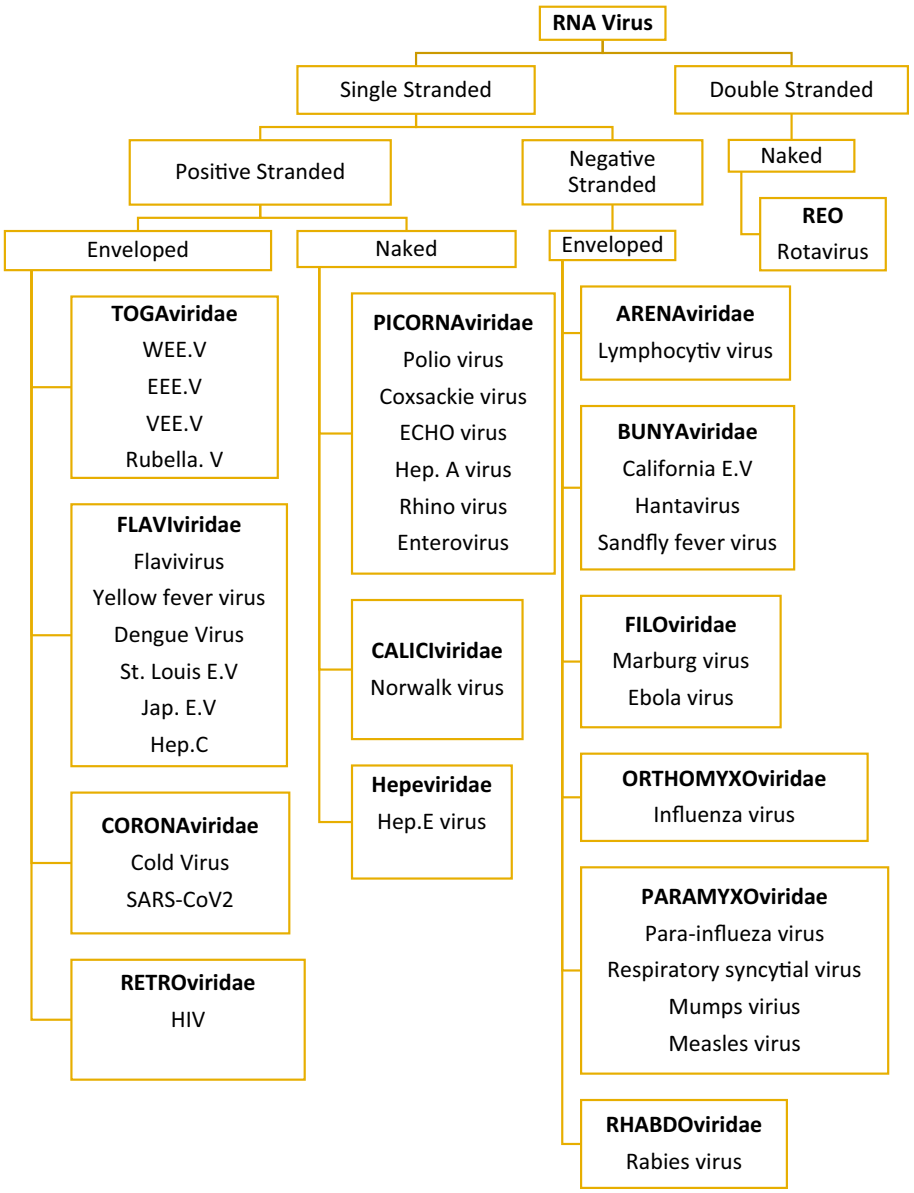


FIGURE 6.1 Relative size of the virus.

by host ribosomes in the cytoplasm. First, RNA-dependent RNA polymerase is made from a positive strand viral genome; then this RNA-dependent RNA polymerase is used to make negative strands. Negative strands are used as a template for making more positive-stranded RNA, and positive strands are used to make viral proteins, including RNA-dependent RNA polymerase.

The negative-strand RNA virus cannot use negative-strand RNA to make viral proteins. Instead, it must be transcribed into positive strand with the help of viral enzymes, RNA-dependent RNA polymerase, which the virus must carry with them. Retrovirus is the exception because it transcribes RNA into DNA in the reverse direction with the help of the enzyme reverse transcriptase, which is RNA-dependent DNA polymerase and is carried by the virus. Once viral DNA is made, it enters into the host nucleus and fuses with the host DNA with the help of viral enzyme integrase and forms provirus. In the nucleus, viral genes are expressed, leading to the production of mRNA, which enters into the cytoplasm and is translated into viral proteins. Finally, these viral proteins and genome assemble into virions and buds out to infect new cells.

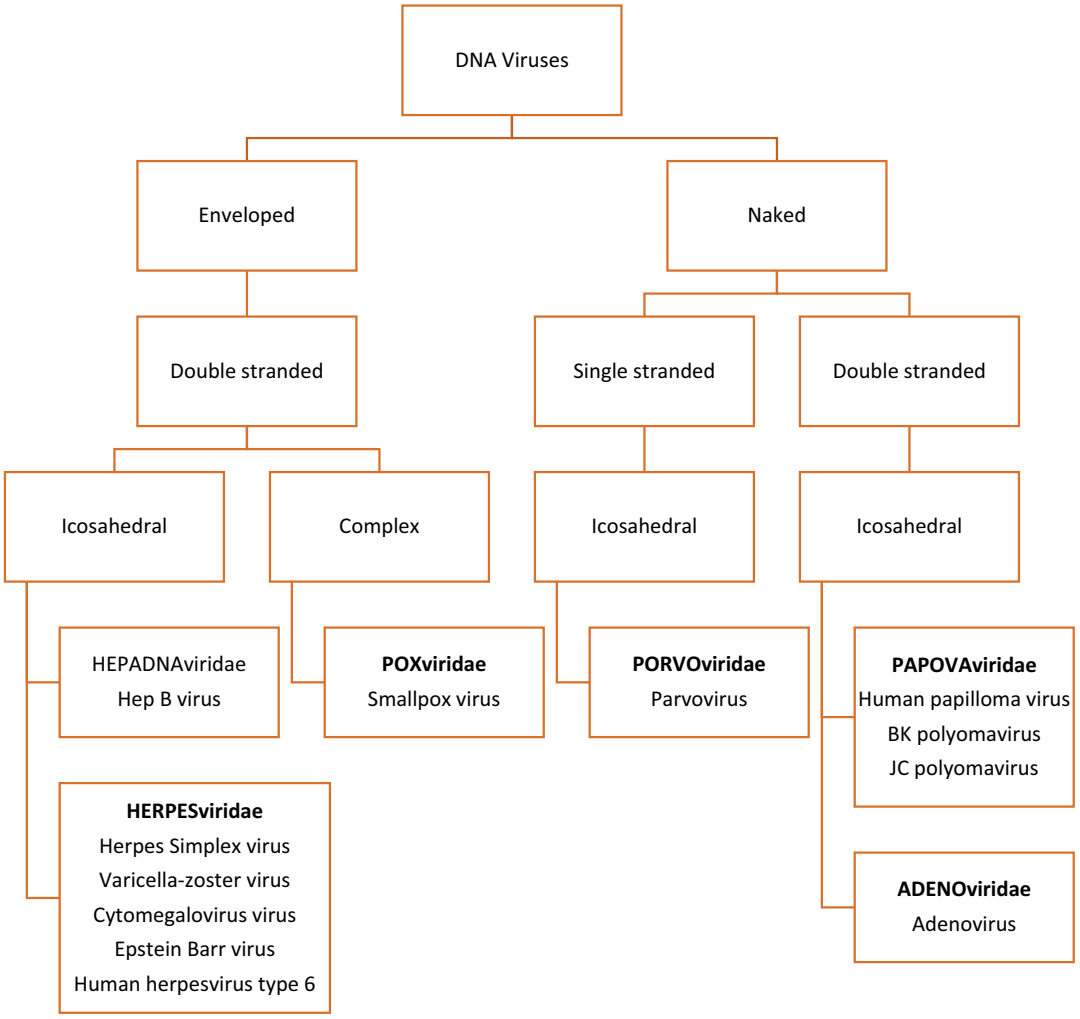


WEE= Western Equine Encephalitis virus
EEE= Eastern Equine Encephalitis virus
VEE= Venezuela Equine Encephalitis virus
E.V = Encephalitis virus
Jap E.V = Japan encephalitis virus
HIV = human immunodeficiency virus

6.2.2 DNA viruses

Most DNA viruses are double stranded and have both positive and negative strands except parvovirus, which has single strand. In DNA viruses, negative strands are read while positive strands are ignored. Once DNA viruses enter the host cell, it migrates into the nucleus, where transcription occurs. In early transcription, mRNA is transcribed, which encodes for enzymes and proteins needed for DNA replication. After DNA replication, viral mRNA along with host mRNA are transcribed in the nucleus and migrates to the cytoplasm and where they are translated into the viral proteins.

Some of the viral DNA integrates into host DNA called provirus. These viruses replicate along with host DNA and produce viral progeny. This is known as lysogenic cycle and results in latent infection. A latent infection may change to active infection in response to the host environmental condition in which lysogenic cycle change to lytic one. This results in the destruction of the host cells and production of more viruses and acute or active infection. It is known that proviruses account for about 8% of human genome.



Clinically, virus infection can be categorized by the organ system they infect. Most common viral infection and type of viruses are as follows (Fig. 6.2)

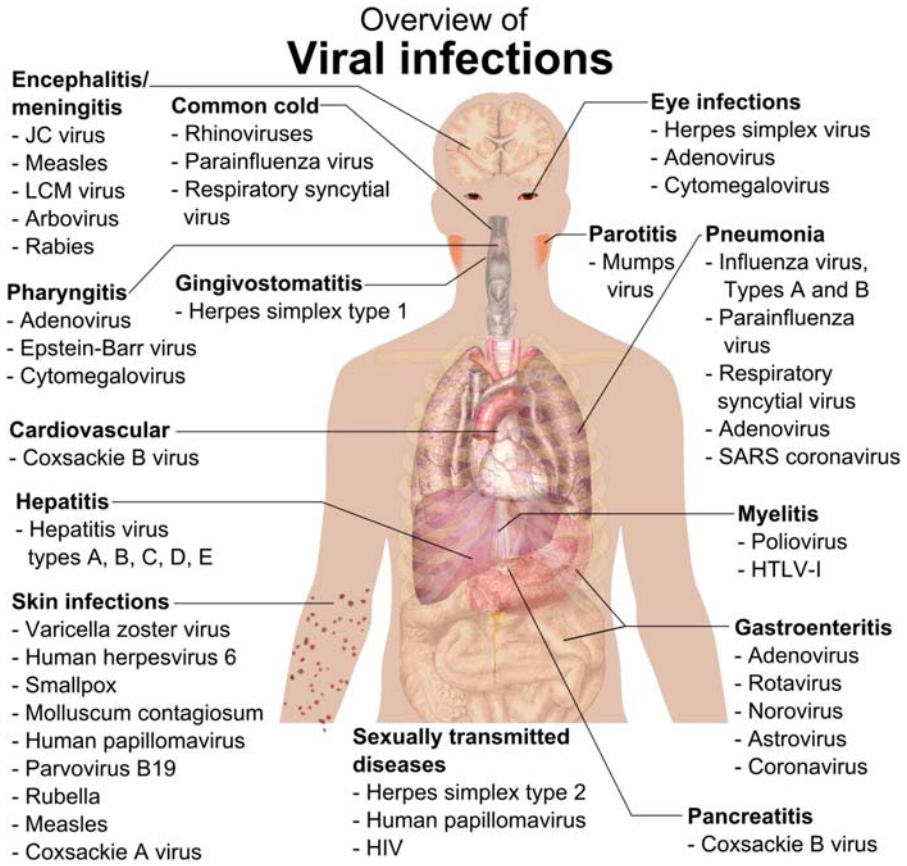


FIGURE 6.2 Viral infections. *Source: Wikipedia commons.*

6.3 Respiratory viruses

Respiratory viruses (RNA and DNA) include viruses that enter the human host via respiratory droplets such as coughing, sneezing, touching contaminated items, and then touching the eyes and nose.

Respiratory viruses includes:

- Influenza virus
- Parainfluenza virus
- Adenovirus
- Respiratory syncytial virus
- Rhinovirus
- Coronavirus
- Mumps

6.3.1 Influenza virus

- Responsible for influenza
- Single-stranded, negative-sense RNA virus. Belong to the Orthomyxoviridae family
- Several types, but three are important infect humans.
  1. Type A: most common and cause the most severe infection.
  2. Type B: Less common and hardly mutate. It only infects human.
  3. Type C: Rare and only infect humans and pigs. Does not mutate.
- Type A is further classified into subtypes depending upon the two glycoproteins on the surface of viral enveloped.
  - Haemagglutinin A (HA) → binds to the sialic acid on the surface of the host cells and fuses with the host cell membrane. There are 17 different types of haemagglutinin (H1 to H17)
  - Neuraminidase (NA) → enzymatically cleaves sialic acid and helps release virions into the host cells. There are nine different types of neuraminidase (N1 to N9)
- Various subtypes of type A, but the most common are H_3N_2 and H_1N_1
- H_1N_1 also called swine flu or Spanish flu originated from pigs.
- H_5N_1 and H_7N_9 are avian flu.
- The virus enters the human body via respiratory route. It multiplies in respiratory mucosa and causes cellular destruction and inflammation.
- Antibodies IgG and IgA and T cells play an important role in fighting the infection.

6.3.1.1 Influenza

(Please also see Section 9.1.1.5)

- Outbreak → October to April or winter season.
- Signs and symptoms of influenza vary, but the most common symptoms are fever, chill, cough, pain, headache, coryza, and stuffy nose ± GI symptoms.

Complications:

- Otitis media in children
- Pneumonia in seniors and patients with chronic medical conditions
- Encephalitis

Risk factors:

- Children ages 2–5 years
- Adult >65 years
- Patients with chronic medical conditions or immune-compromised
- Pregnant women

Diagnosis:

- Mostly clinical
- Rapid influenza test
- PCR

Differential Diagnosis

- COVID-19
- Pneumonia
- Respiratory syncytial virus (RSV) infection
- Parainfluenza viral infection

Treatments:

- Supportive, rest, and increase fluid intake
- Acetaminophen for fever or pain, decongestant for stuffy nose
- Antivirals for high-risk patients with onset of symptoms are not more than 2 days. These antivirals decrease the duration of infection couple of days and decrease the severity of the symptoms if started early.
  - Neuraminidase inhibitors
    Inhibit the release of virus from the infected cells. Only effective if starts within 48 h from the onset of symptoms. It decreases the duration of infection to a few less days.
    Oseltamivir → oral form
    Zanamivir → nasal inhalation
    Peramivir → IV
  - Endonuclease inhibitors:
    Stop viral replications by blocking the viral enzyme, RNA transcriptase.
    Baloxavir
  - Use of amantadine and rimantadine is no longer recommended due to high rate of resistance.
  - Vaccine: decrease the risk of catching flu to one-half.
  - Two types
- Live attenuated, which is given intranasally (LAIV)
- Inactivated: trivalent and quadrivalent, which also covers type B.
- High-dose vaccine is available to seniors ages >65 years.
- LAIV: should not be given to high-risk patients, pregnant women, immune compromised patients, and children.
- Flu vaccine is developed on chicken eggs and should be used cautiously in patients with egg allergies. Some cases of Guillain–Barre syndrome have been reported with the use of vaccines and should be avoided in patients with a history of the reaction.

6.3.1.1.1 Reye's syndrome

- Reye's syndrome is associated with using aspirin in children during viral or bacterial infection, especially in influenza B and varicella viral infection.
  Pathophysiology of Reye's syndrome is poorly understood. It is proposed that the hypersensitivity response to aspirin involves in mitochondrial injury, inhibiting oxidative phosphorylation and fatty acid beta-oxidation in liver cells. This results in the build-up the ammonia.
- Signs and symptoms start 3–5 days after afebrile illness resolves. Sudden onset of protracted vomiting, mental status changes, increased intracranial pressure, hepatomegaly, liver failure, seizure, coma, or death. There is no specific treatment. Symptomatic treatment is recommended and avoid use of aspirin in children during viral or bacterial infection.

6.3.2 Parainfluenza virus

- Single-stranded, negative-sense, enveloped RNA viruses belong to a family of paramyxoviridae.
- Four subtypes → 1, 2, 3, 4
  - Types 1 and 2 cause croup in children
  - Type 3 causes pneumonia and bronchiolitis
  - Type 4 is rare and causes a mild infection
- Mostly infect children under 5 years old.
- Outbreak in autumn
- The viral lipid membrane has two glycoproteins hemagglutinin-neuraminidase (HN) and fusion (F) protein. HN is used to bind to sialic acid on the surface of the epithelial cells, while F protein helps the virus to fuse with the host cell membrane.
- Once inside the host cell, RNA polymerase transcribes negative-sense RNA to positive-sense mRNA, which is translated by the host ribosome into viral proteins.
- Risk group:
  - Children ages 6 months to 3 years
  - Patients with asthma
  - Patients with intubation.

6.3.2.1 Croup

- Croup is the inflammation of the larynx, trachea, and bronchioles, which result in difficulty in breathing. It causes barking cough, hoarseness, strider, and high pitch whistling sound. Coarse may result in fetal outcome. Emergency treatment is needed.
- Diagnosis
  - Clinical
  - Neck X-ray → steeple sign see google image library
  - Reverse transcription polymerase chain reaction test (RT-PCR)

- Differential diagnosis
  - Acute epiglottitis
  - Bacterial tracheitis
  - Peritonsillar abscess
  - Foreign body aspiration
  - Angioedema

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- Treatment:
  - Corticosteroid IV/oral/nebulizer
  - Epinephrine
  - Oxygen
  - Ventilation if needed
  - No vaccine is available.

6.3.3 Adenovirus

- Double-stranded, naked, icosahedral capsid, DNA virus.
- There are more than 100 serotypes; 49 infect humans.
- Cause common cold, sore throat, pneumonia, conjunctivitis, gastroenteritis, and hemorrhagic cystitis
- Mostly infect children and immune compromised patients involving multiple organs.
- Serotypes 3, 4, and 7 are responsible for outbreaks of acute respiratory disease in military recruits.
- Incubation period is usually 2–14 days. Virus may remain latent in renal parenchyma and other tissue and reactivated in immunocompromised patients.
- Some adenoviruses (Ad12) are associated with tumor formation.
- Adenovirus genome is used as a vector in experimental gene therapy.
- Transmission:
  - Respiratory droplets
  - Contaminated water and fecal–oral route
  - Flies
  - Touching infected surface and then touching nose, mouth, or eyes
- Diagnosis:
  - Clinical
  - PCR
  - Culture

- Treatment:
  - Symptomatic treatment
  - Cidofovir or immunotherapy for immune compromised patients.

6.3.4 Respiratory syncytial virus

- Single-stranded, negative-sense RNA virus that belongs to a family of Paramyxoviridae.
- Cause of bronchiolitis and pneumonia in infants and young children.
- Most common cause of bronchiolitis in children <5 years old.
- This virus causes fusion of respiratory epithelial cells to form large multinucleated cells called syncytial; therefore, this virus is as named respiratory syncytial virus.
- Risk factors:
  - Premature babies
  - Babies who are not breastfeed
  - Babies with a neuromuscular disorder
- Sign and symptoms: Start with upper respiratory symptoms with fever which progress to dyspnea, wheezing, cough, crackles, and leads to bronchiolitis and pneumonia mostly in children of <6 months old, elderly patients, immunocompromised, or those having underlying risk factors.
- Diagnosis:
  - Viral antigen test
  - RT-PCR
  - Culture
- Treatment:
  - Treat the symptoms
  - Oxygen
  - Inhale ribavirin
  - Palivizumab, a monoclonal antibody against RSV F protein, can be used for prophylaxis in high-risk infants.
  - No vaccine is available

6.3.5 Rhinovirus

- Single-stranded, positive sense RNA virus belongs to a family of Picornaviridae.
- Over 100 serotypes are known and all cause cold.
- Rhinovirus is the most common cause of cold.
- Transmission is via respiratory routes such as sneezing, coughing, and nasal secretion.
- Risk factors:
  - Young children
  - Elderly
  - Immunocompromised or patients with debilitating conditions such as asthma, chronic obstructive pulmonary disease, or cystic fibrosis.

- Signs and symptoms of cold:
  - Rhinorrhea, nasal congestion, cough, sore throat, headache, and malaise.
  - Self-limited in 7−10 days
- Diagnosis:
  - Clinical
  - PCR
  - Culture
- Treatment → Symptomatic, analgesic, and antipyretic ± decongestant
- Vaccine: Not available.

6.3.6 Coronavirus

- The word corona is a Latin word meaning "crown" refers to the characteristic appearance of the virus under the electron microscope.
- Single-stranded, positive-sense enveloped RNA virus which belongs to a family of Coronaviridae and a large family of viruses that causes illness ranges from mild common cold to more severe infections such as COVID-19.
- Responsible for 1/3 cases of upper respiratory tract infection and 15% cases of common cold worldwide.
- Tropism: epithelial cells. Human coronavirus infects epithelial cells of the respiratory tract, while animal coronavirus usually infects epithelial cells of digestive tract.
- Infect both humans and animals.
- Seven strains of human coronaviruses are known. Four strains produce mild symptoms, while three produce potentially severe symptoms, which include the following:
  - SARS-CoV-2 → COVID-19 (severe acute respiratory syndrome coronavirus 2)
  - MERS-CoV → Middle East respiratory syndrome-related coronavirus
  - SARS-CoV → Severe acute respiratory syndrome coronavirus.

6.3.6.1 COVID-19

- Global pandemic
- Most people have mild symptoms, and about 20%−50% of patients are asymptomatic.
- Initially, it starts with an upper respiratory infection, which may deteriorate, especially in high-risk patients, to lower respiratory infection and acute respiratory distress syndrome (ARDS).
- Signs and symptoms:
  - Fever, cough, fatigue, headache, sore throat, ± loss of sense of smell or taste, ± diarrhea.
  - Reason unknown, in some patients or patients with comorbidity, symptoms deteriorate to dyspnea, hypoxia, extensive lung damage, multiorgan failure, and death.

- Risk factors:
  - Obesity
  - Diabetics
  - Hypertension
  - Age → elderly patient
  - Respiratory disease
  - Cancer
  - Cardiovascular disease
  - In pediatric patients, it may cause pediatric inflammatory multisystem syndrome, resulting in dilation and inflammation of blood vessels and increase the risk of stroke.
- Complications:
  - ARDS
  - Septic shock
  - Pulmonary embolism
  - Stroke
  - Multiorgan failure
- Diagnosis:
  - RT-PCR
  - Chest X-ray
  - Isothermal amplification test
  - Viral RNA → CRISPR directly tag viral RNA
  - Viral antigen test
  - Antibody test
- Treatment:
  - Isolation and supportive treatment
  - Hospitalization for moderate to severe symptoms
  - Remdesivir for patients who need low-flow oxygen. It shortened the duration and decreased the mortality rate in some patients.
  - Patients with high-flow noninvasive oxygen → dexamethasone + remdesivir
  - Patient with invasive mechanical ventilation → dexamethasone.
  - Jk1 and JK2 inhibitors (JAK):
    - Janus kinase is a family of intracellular nonreceptor protein tyrosine kinase. These proteins are involved in vital cellular functions such as signaling, growth, and survival. They are also involved in the phosphorylation of key proteins that are required for signal transduction that leads to immune activation and inflammation. Inhibitors of JAK prevent this phosphorylation and reduce the inflammation caused by these proinflammatory mediators, such as IL-6. Additionally, some JAK inhibitors, such as baricitinib, have antiviral activity. There are four members in the JAK family, which includes JAK1, JAK2, JAK3, and JAK4. Jak inhibitors are approved for use in autoimmune diseases.

  - Baricitinib is the JK1 and JK2 inhibitor that is approved for the treatment of rheumatoid arthritis. The Food and Drug Administration (FDA) approved the use of baricitinib as emergency use authorization for COVID-19 in hospitalized patients requiring supplemental oxygen, noninvasive, or invasive mechanical ventilation or extracorporeal membrane oxygenation.
  - Tofacitinib is also a JAK inhibitor which is predominantly selective for JAK1 and JAK3 with modest activity against JAK2 and has the same indication as baricitinib and can be switched.
- Interleukin-6 inhibitors (IL-6):
  - ➢ IL-6 is one of the proinflammatory cytokines produced by various cells and associated with systemic inflammation and respiratory failure. Blocking the IL-6 decreases the severity of the COVID-19.
  - ➢ Recommended in hospitalized patients requiring high-flow oxygen, noninvasive ventilation, or mechanical ventilation. Use with dexamethasone.
  - ➢ Sarilumab, tocilizumab → Interleukins-6 receptor antibodies.
    FDA → approved, NIH → Not enough data.
  - ➢ Siltuximab → interleukin-6 monoclonal antibodies.
    FDA → No, NIH → No
- Antiviral monoclonal antibodies
  - These are the antibodies that attach to the viral epitope on the spike protein receptor on the virus and inhibit the virus from infecting the human cells.
  - Recommendation is for mild to severe disease in nonhospitalized patients with high risk of disease progression.
  - Includes:
    - ➢ Casirivimab + Imdevimab → all variants except Omicron.
    - ➢ Bamlanivimab + Etesevimab → all variants except Omicron.
    - ➢ Sotrovimab → all variants including Omicron.
- Antiviral
  - Molnupiravir (PO): Nucleoside, prodrug which is phosphorylated to nucleotide and inhibits replication by incorporation into viral RNA polymerase.
  - Recommendation is for mild to moderate disease, nonhospitalized patients and is not at high risk of disease progression
  - Use for 18 years and up
  - Prevent hospitalization in about 1 in 35
  - Nirmatrelvir + Ritonavir (Paxlovid) → Combination of two antivirals.
  - Nirmatrelvir is a protease inhibitor and inhibits SARS-CoV-2 main protease (Mpro) preventing viral replication. Ritonavir is a human immunodeficiency virus (HIV)-1 protease inhibitor but has no activity against SARS-CoV-2 Mpro. However, ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentration of the nirmatrelvir.
  - Approved for ages 12 and up.
  - Prevent hospitalization in about 1 in 18.

- Convalescent plasma:
  - Clinical studies have not shown mortality benefit or clinical improvement in the use of convalescent plasma.
  - FDA approved high titers convalescent plasma for emergency use in hospitalized or out-patients with impaired immunity.
  - NIH → insufficient data.
  - Possibility of transfusion reaction, allergic reaction, fluid overload, cardiac issue, and acute lung injury.
- Vaccine is approved
- Washing hands and wearing the mask.
- Social distancing

6.3.6.1.1 Management of nonhospitalized adults with COVID (Table 6.1)

Table 6.1 Management of out-patient adults with COVID.

Patient disposition	First choice	Second choice
Patient is symptomatic with high risk of progression to severe COVID-19	Ritonavir—nirmatrelvir (oral) Remdesivir (IV)	Bebtelovimab (IV) Molnupiravir (PO)

6.3.6.1.2 Management of inpatient adults with COVID (Table 6.2)

Table 6.2 Inpatient management of adults with COVID.

Hospitalized patients with mild to moderate disease and does not require supplemental oxygen	The panel recommend against the use of dexamethasone or remdesivir.	High-risk patients use remdesivir
Hospitalized patient requires supplemental Oxygen	Remdesivir or Remdesivir+dexamethasone or Dexamethasone	Patients with rapidly increasing oxygen needs and systemic inflammation add baricitinib (PO) or tocilizumab (IV) in first choice treatment.
Hospitalized patients require Oxygen through high-flow device or NIV	Dexamethasone Dexamethasone + remdesivir	Add baricitinib (PO) or IV tocilizumab if rapidly increasing oxygen needs
Hospitalized patients require MV or ECMO	Dexamethasone + tocilizumab (IV)	Dexamethasone + sarilumab

ECMO, extracorporeal membrane oxygenation; *MV*, mechanical ventilation; *NIV*, noninvasive ventilation.
Source: National Institutes of Health.

6.3.6.2 Drugs table for COVID-19 (Table 6.3)

Table 6.3 Drugs used in COVID-19.

Drugs	Dosage (adult)	Dosage (children)	Dose adjustment	Side effects	Preg
Molnupiravir PO	800 mg q12h × 5 days	None	None	Diarrhea, nausea, headache, dizziness, rash	No data
Nirmatrelvir-ritonavir PO	300—100 mg bid × 5 days	>12 years, same as adult	eGFR 30—60 ↓dose to $^1/_2$ Niramatrelvir	Diarrhea, nausea, Dysgeusia, hypertension, myalgia, ↑hepatic enzymes	No data
Remdesivir IV	200 mg × 1, then 100 mg q12h × 4 days	>12 yrs, same as adult <12 yrs 5 mg/kg × 1, then 2.5 mg/k × 4 days	None	Hypersensitivity, hypotension, nausea, vomiting, ↑liver enzymes	No data
Monoclonal antibodies					
Casirivimab —Imdevimab Not use for Omicron	600 —600 mg × 1 time dose	>12 yrs. Same as adult	None	Fever, chill, nausea, headache, dizziness, bronchospasm, angioedema, hypotension, rash, myalgia	No data
Sotrovimab, also use for Omicron	500 mg IV × 1	>12 yrs. Same as adult	None	Fever, breathing problem, chills, fatigue, arrhythmia, hypo or hypertension, allergic reaction, rash, dizziness	No data
JAK inhibitors					
Baricitinib PO	4 mg po daily × 14 days	>9 yrs. Same as adult dose. Ages 2 —9 yrs, 2 mg daily <2 yrs→ No	eGFR< 60 → 2 mg < 30 → 1 mg < 15 not recommended	Opportunistic infection, lymphoma, thrombosis, ↑liver enzymes, neutropenia, anemia, ↑lipid profile	No data
Tofacitinib	10 mg q12h × 14 days	None	eGFR <50 → 5 mg q12h	Same as above	No data
IL-6 inhibitors					
Tocilizumab	8 mg/kg max 800 mg × 1 dose. May repeat	>2 yrs old. same does as adult. 8 mg/kg	None	Opportunistic infection, GI perforation, hepatotoxicity, neutropenia, thrombocytopenia, demyelination, malignancy	No data

CrCl, creatine clearance; *eGFR*, estimated glomerular filtration rat; *GI*, gastrointestinal; *Preg*, pregnancy category; *yrs*, years.

6.3.6.3 Additional information about COVID-19

History: The COVID-19 pandemic was first reported in December 2019 in mainland China. In the United States, the first case was reported in Washington state in January 2020. Since then, millions of people have been infected. Lockdown and traveling restrictions have tolls on every person. It was a huge challenge for humankind. People and countries are still recovering from the aftermath of COVID-19, which is not over yet.

The virus that caused the COVID-19 pandemic is called SARS-COV-2; it is belongs to a family of coronavirus that usually causes the common cold. However, some strains of coronavirus are associated with the SARS outbreak in 2003 and MERS in 2012. COVID-19 virus is a single-stranded positive RNA enveloped virus. The single-strand RNA is bounded to protein N called nucleocapsid. The virus is enclosed by lipid bilayer which is called envelope. Several proteins are anchored on its envelope and responsible for the virulent effect.

S-protein (spike protein) on the surface of viral envelope binds to the ACE2 receptor on human cells. The enzymes on host cell membrane called catheter L and TMPRSS2 prime the spike protein S and activate the virus to enter the host cell by membrane fusion or endocytosis. Once inside the cell, the positive-stranded RNA translates viral proteins using the host ribosomes. First, RNA polymerase is made by translating the gene of replicase protein on positive RNA strand, and then RNA-dependent RNA polymerase mediates and translates the rest of the structural and nonstructural proteins. A negative strand is made from the positive strand and is used to make more positive strands. All structural and nonstructural proteins are directed to the endoplasmic reticulum for final modification. Positive RNA strands and viral proteins assemble all together and form new virions and bud out through a process of exocytosis to infect other cells.

6.3.6.4 COVID-19 testing

Three types of tests are available in the market for COVID infection:

A. Nucleic Acid Amplification Test (NAAT): Tests the genetic material of the virus. Nasal or pharyngeal swab is taken and tested for the genetic material of SARs-COV-2. It uses RT-PCR and is very accurate, but it takes longer time to get the result.

B. Antigen testing: Detects antigen present on the surface of the viral envelope. It is fast and patients get the result in minutes. However, it is not very accurate. Sensitivity is 60% and specificity is 98%. Most commercially available quick tests are based on it.

C. Antibody tests: Based on detecting specific antibodies the body produced once infected. This test tells that if someone has a past infection. It is not used for diagnosis of current infection.

When to do testing:

1. Exposed to someone who is tested positive at least 5 days after the exposure
2. Feel sick, having symptoms
3. Traveling
4. Going to school or working at school

6.3.6.5 Vaccine for COVID-19

Vaccine is a suspension or solution of inactive or live attenuated bacterial or viral antigen rendered nonpathogenic, injected into the human body to activate the immune response and produce antibodies against the particular bacteria or virus.

Toxoid: Toxoid is an inactive or nontoxic bacterial toxin that can be used to stimulate the production of antibodies.

Traditionally, vaccines are prepared in a lengthy process. Inactivated bacteria or viruses, attenuating live bacteria or virus, or any antigenic part, are used in these vaccines. It usually takes about 10–15 years to bring a vaccine to market. However, the recent emergence of the COVID-19 pandemic and the urgency of the situation has changed this process and vaccines are developed in a method that has never been used before. The new generation of vaccines are called RNA or DNA vaccines. The advantage of the new approach is that less time is required to bring the vaccine to market, plus it is easy to manipulate according to the dominant strain of bacteria or virus.

Some of these vaccines contain mRNA with viral genetic code for spike protein. The mRNA is coated with lipid nanoparticles for stability and is injected into the muscles. It is taken up by muscle cells, dendritic cells, and macrophages. Once inside the cell, mRNA is translated into viral spike protein and transferred to the cell surface, where it is presented to the immune cells and they mount limited controlled immune response. The immune system will recognize any future exposure and mount a specific response to get rid of the virus.

It is found that the enzymes ribonucleases or deoxyribonucleases inside host cells break down the injected mRNA within few days and surface spike protein disappears in few weeks. However, recent studies have shown that some of the SARS-CoV RNAs are reverse transcribed into DNA and integrated into the genome of infected cells by endonuclease LINE1. Presently, it is not known if this happened to mRNA in vaccines.

Pfizer/BioNTtech and Moderna produce mRNA vaccines. Pfizer vaccine requires to be stored at − 70°C and is stable at a temperature of 2–8°C for 5 days. Require 2 doses 21 days apart. Overall efficacy is 95%. Booster is recommended after 6 months.

Moderna vaccine is stored at − 20°C and is stable at a temperature of 2–8°C for 30 days. 2 doses 28 days apart are required. Booster is recommended after 6 months.

Common side effects reported are some pain, redness at the site of injection, tiredness, headache, muscle pain, and light fever. Rare cases of Guillain–Barre syndrome, anaphylactic, and allergic reactions have been reported, but the rate is very low. Some cases of Bell's palsy were reported, but later on, it was found that the incidence rate is no higher than the general public.

DNA vaccines are prepared by AstraZeneca–Oxford and Janssen–Johnson & Johnson (JJ&J). In these vaccines, DNA molecule instead of mRNA is used. The AstraZeneca vaccine used a modified chimpanzee DNA vector from adenovirus that has not been exposed to humans and does not generate an immune response. The J&J vaccine used cold virus, adenovirus 26 CoV2 DNA. These genetically modified DNA only carries the gene for spike protein of coronavirus. Once injected, it enters the human cells, where it is transferred to the nucleus. In the nucleus, it does not incorporate into the host nucleus; instead it is converted to mRNA. The converted mRNA transfers back to cytoplasm and starts making viral spike proteins with the help of host ribosome. Then these newly formed viral spike proteins migrate to the cell surface and are presented to immune cells. These immune cells are activated, primed, and ready for a future viral infection to mount a specific response.

AstraZeneca–Oxford vaccine requires 2 doses 12 weeks apart and is stable at 2–7°C for 6 months. Janssen–Johnson & Johnson vaccine only requires one shot and can be stored at 2–8°C for 6 months. The efficacies of both vaccines are 70% and 72%, respectively, in the US population. Both these vaccines are associated with rare cases of thromboembolic events, pulmonary embolism, and thrombocytopenia, including Guillain–Barre syndrome in the case of JJ&J vaccine.

Other Vaccines:

Sputnik Vaccine: Made in Russia, based on two different adenoviral vectors Ad 26 and Ad 5. Its mechanism of action is the same as other DNA vaccine made by AstraZeneca and JJ&J. Sputnik vaccine requires two doses 21 days apart. Efficacy is 91.6%. Stored at −18°C liquid form, while the dry form is stable between the temperature of −2 and 8°C.

Sinovac or Coronavax: Made in China. Use inactive virus. Required 2 doses 21 days apart. Efficacy is 65%.

Novavax (NVX): Uses protein subunits of the virus which mimic COVID-19 virus spike protein to stimulate the immune system. It required two doses 4–12 weeks apart. Efficacy is 89.7% in the UK population.

There are several other vaccines that are under development, and in next one or 2 years we will see lot more vaccines on the market.

Variation in the spike protein of the virus may limit the effectiveness of these vaccines. However, they are still effective in being used against these variants

6.3.6.6 Vaccine's summary (Table 6.4)

Table 6.4 Type of available COVID-19 vaccines.

Name of vaccine	Type	Dosage	Storage	Side effects
Pfizer	mRNA	2 doses 21 days apart	−70°C 2−8°C for 5 days	Pain, redness at the site of injection, tiredness, light fever, headache. Rare: Guillain− Barre syndrome, myocarditis, pericarditis
Moderna	mRNA	2 doses 28 days apart	−20°C 2−8°C for 30 days	Pain, redness at the site of injection, tiredness, light fever, headache, Rare: Bell's palsy, Guillain− Barre syndrome, myocarditis, pericarditis
AstraZeneca −Oxford	DNA	2 doses, 12 weeks apart.	2−7°C for 6 months	Pain, redness at the site of infection, tiredness, light fever, headache. Rare: Thrombocytopenia, pulmonary embolism, thrombocytopenia, myocarditis, pericarditis
Janssen −Johnson & Johnson	DNA	One dose	2−8°C for 3 months	Pain, redness at the site of infection, tiredness, light fever, headache. Rare: Blood clots, thrombocytopenia, Guillain− Barre syndrome, myocarditis, pericarditis
NOVAVAX	Protein subunits	2 doses, 4 −12 weeks apart	2−8°C for 6 months	Muscles pain, redness at the site of injection, tiredness, light fever, headache. Rare: Myocarditis
Sputnik	DNA	2 doses, 21 days apart	−18°C (liquid form) −2−8°C (dry form)	Muscles pain, redness at the site of injection, light fever, headache, tiredness
Sinovac or Coronavax	Inactivated virus	2 doses 14 days apart	−2−8°C	Muscles pain, redness at the site of injection, light fever, headache,

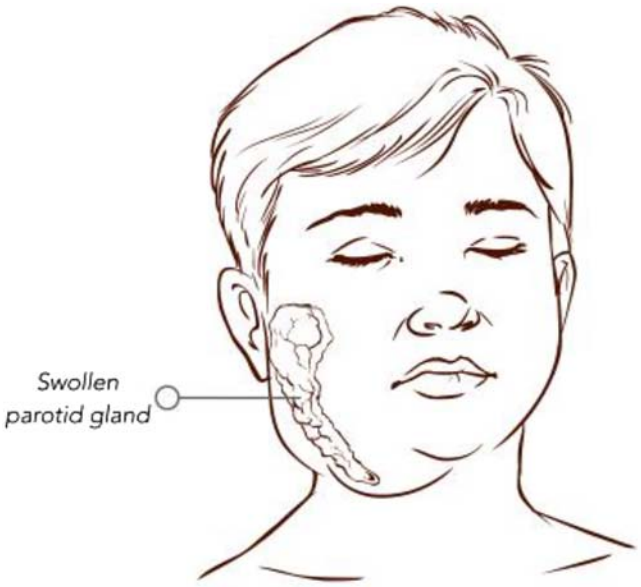
6.3.7 Mumps virus

Single-stranded, negative-sense RNA virus that belongs to a family of Paramyxoviridae
Cause: Mumps

6.3.7.1 Mumps (Fig. 6.3)

- Mumps virus transmits through respiratory droplets or saliva. It replicates in the upper respiratory tract and local lymph node and spreads to salivary glands, especially the parotid glands, via blood.
- Causes swelling and pain of bilateral parotid glands. For some reason, about 25% of patients could develop orchitis.
- Low to moderate grade fever, headache, malaise, and anorexia.
- Complications: Meningitis, encephalitis, pancreatitis
- Report to the public health authority is required
- Diagnosis:
  - Clinical
  - RT-PCR
  - Serologic testing

FIGURE 6.3 Mumps.



- Treatment
  - Supportive
  - Vaccine: MMR
    First dose at the ages of 12–15 months
    Second dose at the ages of 4–6 years

6.4 Viruses associated with gastroenteritis

Please also see Section 9.9 for more information.

- Viruses that cause gastroenteritis are mostly acquired by the fecal–oral route or unhygienic condition. They cause watery diarrhea, vomiting, abdominal pain, ± fever. Symptoms usually resolve within 1 week. Death, especially in infants, is mostly due to dehydration and loss of electrolytes.

6.4.1 Rotavirus

- Double-stranded RNA virus that belongs to a family of Reoviridae. The RNA is surrounded by double-layered, icosahedral capsid without any lipid outer membrane (naked). It has a characteristic wheel-like appearance when viewed under the electron microscope, hence called rota, meaning "wheel."
- There are about eight strains: A-H. Strain H is most commonly responsible for human gastroenteritis.
- Infects young children, especially ages between 6 and 24 months, and young children in daycare.

- Transmission is mostly fecal–oral route.
- Rotavirus secretes nonstructural protein 4, which destroys villi in the brush border of the small intestine. Damaged villi are replaced by immature villi and decrease nutrient absorption, secretion of digestive enzymes, and temporary lactose intolerance.
- Rotavirus activates enteric nervous system, which results in increases electrolyte secretion in the intestinal lumen.
- Incubation period is 24–48 h, and infection may last up to 8–10 days.
- The symptoms usually start with vomiting followed by perfuse watery diarrhea, severe dehydration, and low-grade fever.
- Complications:
  - Severe dehydration
    Seizure
  - Intussusception
  - Intestinal obstruction
- Diagnosis:
  - Clinical
  - Viral antigen in stool
  - PCR or RT-PCR
- Treatment:
  - Hydration
  - Electrolytes
  - Hygiene and sanitation
  - Vaccine for rotavirus → two vaccines are approved in the United States, and both are used orally. Vaccines provide 85%–98% protection against severe illness and 74%–87% protection against illness of any severity.
  - RotaTeq: Given in three doses at ages 2, 4, and 6 months
  - Rotarix: Two doses at ages 2 and 4 months.
  - Rare cases (1 in 20,000) of intussusception have been reported with the use of vaccine.

6.4.2 Norovirus

- Single-stranded, positive-strand, naked mRNA virus that belongs to a family of Caliciviridae.
- The virus is named after the city of Norwalk, Ohio, where an outbreak occurred in 1968.
- There are several strains of norovirus, but only strains I, II, and IV cause illnesses in humans.
- Viruses enter the human cell via the host cell's endocytosis and make long polyprotein using host ribosomes. Protein is broken down into small proteins by viral proteases.

- Infects both children and adults, especially people in cruise ships, nursing homes, hospitals, schools, military barracks, and prisons.
- Transmission is fecal to oral route, contaminated water, food supply, and person to person.
- Incubation period is 12–48 h and illness usually lasts 48–72 h.
- Signs and symptoms are as follows:
  - Nausea
  - Vomiting
  - Diarrhea → nonbloody and watery
  - Stomach pain
  - Fever
  - Headache
  - Body aches and malaise.
- Complications:
  - Enteropathy
  - Intestinal villous atrophy
  - Malabsorption
- Diagnosis:
  - Clinical
  - Viral antigen in stool
  - PCR or RT-PCR
- Treatment:
  - Hydration
  - Electrolytes
  - Hygiene and sanitation
  - No vaccine is available

6.4.3 Adenovirus → usually infects infants. See Section 6.3.3

6.4.3.1 Astrovirus

- Astro means "star" in Latin and refers to star-like appearance under the electron microscope.
- Belongs to a family of Astroviridae, single-stranded, positive-sense, naked, icosahedral mRNA virus.
- Infects birds and mammals, several serotypes; types 1–8 infect humans.
- Transmission is fecal oral route.
- Mostly cause gastroenteritis in children with underdeveloped immune systems and immunocompromised elderly patients.
- Symptoms start with diarrhea followed by vomiting, fever, malaise, and abdominal pain.
- Incubation period is 3–4 days. Symptoms are usually not very severe and subsidized in 2–4 days without any intervention.

- Diagnosis:
  - Electron microscopy
  - Enzyme-immunoassay (ELISA)
  - RT-PCR
- Treatment:
  - Hydration
  - Electrolytes
  - Antivomiting

6.5 Exanthematous viruses

- Includes class of viruses transmitted via respiratory droplets, has affinity for respiratory cells, and causes skin manifestations. These include the following:
- Rubeola virus
- Rubella virus
- Human parvovirus B 19
- Human herpes virus type 6 and 7
- Smallpox virus
- Monkeypox virus

6.5.1 Rubeola virus

- Single-stranded, negative-sense RNA virus, which belongs to a family of Paramyxoviridae.
- Highly infectious virus.
- Hemagglutinin (H) protein on the surface of measles virus binds to the target receptor of the host cells, and F protein helps the virus to fuse with the host cell membrane and enter inside the cell.
- Inside the host cell's cytoplasm, negative-sense mRNA transcribes to positive-sense mRNA with the help of RNA polymerase.
- Positive-sense stranded mRNA translates viral proteins, assembles into virions and buds out, killing the host cells.
- Responsible for measles.

6.5.1.1 Measles (Fig. 6.4)

- Highly infectious disease and the leading cause of death in young children
- Spreads via air droplets or touching infected surface and spreads to the nose, mouth, or eyes.
- Infects multiorgan systems in the body
- Incubation period is 10–14 days
- Stages: four stages:

1. Prodrome: Start with high fever, cough, conjunctivitis, coryza, and stuffy nose.
2. Enanthem phase: Starts 1−2 days later. Rash on mucus membrane inside the cheeks called Koplik spot
3. Exanthem phase: Red, blotchy, maculopapular rash starts on the head and goes down to the feet.
4. Recovery phase: Rash starts fading away. Persistent cough continued for a month.

- Contagious period:
  1−2 days before prodrome through exanthem phase and continues 4 days after the onset of rash.
- Infection results in lifelong immunity
- Complications:
  - Pneumonia
  - Encephalitis
  - Bacterial superinfection
  - Subacute sclerosing panencephalitis, which can occur in 7−10 years later
  - Acute thrombocytopenic purpura
- Risk factors:
  - Unimmunized children
  - Immunocompromised patient
  - Underdeveloped countries
- Diagnosis:
  - Clinical →Fever, rash, and Koplik spot
  - Serological → IgM antibodies in serum. IgG is highly accurate but takes a longer time to develop.
  - RT-PCR of the throat or nasopharyngeal swab
- Treatment:
  - Supportive.
  - Vitamin A for children has been shown to decrease complications.
  - Patient dies due to complications of pneumonia and encephalitis
  - Vaccine
    MMR → live attenuated vaccine is given at the ages of 12−15 months then a booster is given at 4−6 years of age.
    Contraindication: Immunocompromised patient with $CD_4 < 15\%$
- Postexposure prophylaxis:
  - Give vaccine within 3 days
  - If the vaccine cannot be given, immunoglobulin can be used within 6 days of postexposure. Do not give the vaccine for 5−6 months after giving immunoglobulin
  - Quarantine the patient

FIGURE 6.4 Measles. *Source CDC.*

6.5.2 Rubella virus

- Single-stranded, positive sense with icosahedral capsid RNA virus that belongs to Togaviridae family.
- Virus is transmitted through respiratory droplets, enters into respiratory epithelial cells where it replicates, and spreads out to other parts of the body via lymphatic and blood vessels.
- Cause German measles

6.5.2.1 German measles (Fig. 6.5)

- Infects children and adults
- Part of TORCH
- Symptoms are milder than measles and include the following:
  - Low-grade fever
  - Rashes are similar to measles but less extensive and fade away in 3 days. Rashes start on the face and spread to the trunk and extremities
  - Characteristic swelling and painful suboccipital, postauricular lymphadenopathy.
- Infection in pregnant women causes complications in the fetus, which include the following:
  - Hearing lost
  - Cataract and retinopathy
  - Encephalitis
  - Stillbirth or spontaneous abortion
  - Congenital heart defects
  - Extramedullary hematopoiesis results in red and blue spots on the skin → blueberry muffin rash baby.
  - Chances of congenital defect increase if the pregnant women are infected anywhere between 4 weeks before and 20 weeks after conception. Infection after 20 weeks usually does not cause fetal defects but may result in intrauterine growth restriction.

T = Toxoplasmosis
O = Others like syphilis
R = Rubella
C = Cytomegalovirus
H = Herpes simplex

www.images.google.com "German measles"

- Risk factors:
  - Unvaccinated children
- Diagnosis:
  - Enzyme assay
  - PCR
- Vaccine: MMR

FIGURE 6.5 German measles. *Source CDC (PHIL).*

6.5.3 Human parvovirus B19

- Single-stranded, smallest DNA virus, which belongs to the Parvoviridae family. Capsid is icosahedral in shape and naked.
- Transmission is via respiratory droplets, blood transfusion of infected blood, and placental transmission to the fetus.
- Virus reaches bone marrow where it infects proerythroblast and starts to replicate there. The virus produces nonstructural protein 1 or NS1, which is toxic and causes apoptosis or cell death and results in severe anemia in patient with underlying conditions such as sickle cell anemia, thalassemia, and hereditary spherocytosis.
- Cause erythema infectiosum (fifth disease)

6.5.3.1 Erythema infectiosum (fifth disease) (Fig. 6.6)

- Starts with nonspecific flu-like symptoms and then several days later develops maculopapular rashes on the cheek (slap cheek) and spreads to extremities.
- Infects both children and adults.
- Infects progenitor cell of RBC in the bone morrow
- Causes aplastic crises in patients with hemoglobinopathies, HIV, and immunocompromised patients.
- Infection in pregnant women may result in anemia in fetus, hydrops fetalis, or intrauterine death.
- Adults may develop joint pain and inflammation that symmetrically affect small joints of hands, feet, and knees
- Risk factors:
  - Direct contact with infected person
  - Respiratory droplet

FIGURE 6.6 Fifth disease. *Source CDC Public Health Image Library.*

- Diagnosis:
  - Clinical
  - Serological testing
  - PCR
- Treatment
  - Supportive
  - Blood transfusion in aplastic crises
  - Vaccine → Not available
  - Chronic infection in immunocompromised patients is treated with immune globulin.

6.5.4 Human herpes virus type 6 and 7

- Double-stranded DNA virus that belongs to Herpesviridae family. It has icosahedral capsid which is enclosed by envelopes (lipid membrane).
- Initially, the virus enters in human respiratory epithelial cells via respiratory droplets and survives and replicates efficiently in CD4+T cells.
- Human herpes virus (HHV)-6 remains latent in lymphocytes and monocytes after the primary infection.
- Cause of about 15%–45% of febrile illnesses in infants
- Responsible for roseola infantum.

6.5.4.1 Roseola infantum

- Infects young children of 6 months to 2 years of age.
- Incubation period is 10–15 days
- Starts with a high fever, which lasts 3–5 days, and then develops maculopapular rashes on the chest and abdomen, which last 2–3 days and go away on its own. The child appears well.
- Other symptoms like periorbital edema and lymphadenopathy may be present.
- Complications:
  - Febrile seizure
  - Encephalopathy in immune compromised patient
- Risk factors:
  - Age <2 years
  - Immunocompromised
- Diagnosis:
  - Clinical
  - Serological
  - Culture
  - PCR
- Treatment:
  - Supportive
  - Self-limiting
  - No vaccine available

Difference between roseola infantum and measles rash:

Roseola Infantum	Measles
Start with fever.	Start with rash.
Rash mostly on Chest and Abdomen	Rash start on face, and spread downward

- HHV-6 is also associated with otitis media and encephalitis in immunocompromised patients

6.5.5 Smallpox virus

- Highly contagious virus
- DNA double-stranded, complex virus that belongs to Poxviridae family, genus *Orthopoxvirus*, and species *Variola* virus.
- There are two variants of the *Variola* virus that cause smallpox:
  - Variola major
  - Variola minor
    - Variola minor is a milder form of smallpox than variola major. Last case was observed in Somalia in 1977.
- No cases of smallpox have been reported since 1977.
- First disease for which first a vaccine was developed
- Only infects humans.
- Responsible for millions of deaths before 1977
- Transmission:
  - Person to person
  - Respiratory droplets
  - Contaminated clothes or bed sheets.

www.images.google.com
" smallpox"

- Risk factors:
  - Lab workers or health care professionals
  - Exposure during bioterrorism

6.5.5.1 Smallpox (Fig. 6.7)

- Signs and symptoms:
  - Incubation period is 10–12 days
  - Symptoms start with fever, headache, and malaise with ± abdominal pain and vomiting (prodrome). It usually lasts 2–4 days.
  - After the prodrome, first visible lesions are developed on oropharyngeal mucosa called enanthem.
  - Then, maculopapular rashes are developed on the face, trunk, and extremities after 24–48 h.
  - Soon lesions convert to pustules, which, unlike chicken pox, are at the same stages.
  - These papules are filled with opalescent fluid.
  - By the end of second week, pustules deflate and begin drying up.
  - On days 16–20, scabs form and flake off and leave scars.
  - Fatality is about 30%
- Complications:
  - Bronchitis
  - Pneumonia
  - Encephalitis
  - Blindness
  - Osteomyelitis
- Diagnosis:
  - Clinical
  - Microscopic examination of skin biopsy → Inclusion bodies called Guarnieri bodies composed of virus and proteins.
  - PCR
  - Immunosorbent assays (ELISA).
- Treatment:
  - Supportive
  - Smallpox vaccine, if given within 3 days of exposure, will prevent or significantly decrease the severity of the disease.
  - Tecovirimat was approved in 2018 for the treatment of smallpox.
  - Some studies showed that cidofovir might be effective.
  - Brincidofovir was approved in 2021.

6.5.6 Monkeypox Virus

- A double-stranded DNA virus belonging to the family of Poxviridae.
- Monkeypox virus is structurally related to the smallpox virus.
- Although, as the name indicates, monkeypox do infect monkeys and other nonhuman primates, they are not the primary reservoirs for the virus. The specific reservoir is unknown. However, the leading candidates are small rodents.

FIGURE 6.7 Smallpox. *Source CDC (PHIL).*

- Most cases of the infection are reported in Republic of Congo, but sporadic cases have been reported in other parts of the world, including the United States of America and Canada.
- Transmission:
  - Infection to humans is transmitted from direct contact with the infected animal via body fluids, salivary or respiratory droplets, contact with wound exudate, animal bite, or scratch.
  - Person-to-person transmission is also possible via close contact, respiratory droplets, and other body fluids.

6.5.6.1 Monkeypox (Fig. 6.8)

- Sign and symptoms:
  - Incubation period is 7–14 days but can range from 5 to 21 days
  - Initial symptoms start with nonspecific flu-like symptoms such as fever, headache, muscle aches, backache, and swollen lymph nodes, characteristically behind the ear, below the jaw, neck and groin.
  - After a few days of fever, lesions start on the face and distribute to other parts of the body, including the palm of hands and soles of feet.
  - Lesions progress to macules, papules, vesicles, pustules, and scabs before falling off.
  - In each part of the body affected, the lesions evolve in the same stage.

  - Clinical similarity between monkeypox, smallpox, or chickenpox makes the diagnosis difficult. However, presence of lymphadenopathy, preeruptive fever, and slower maturation of skin lesions may support clinical diagnosis of monkeypox than chickenpox or smallpox.
  - The illness typically lasts 2–4 weeks
- Complication:
  - Secondary bacterial infections such as pneumonia, sepsis, encephalitis, or loss of vision if the eye is infected.
  - Still birth or birth defects
- Diagnosis:
  - Clinical
  - PCR
- Treatment:
  - There is no proven treatment
  - Tecovirimat → Approved for the treatment of smallpox can be used.
  - Cidofovir or brincidofovir may also be effective.
- Vaccine:
  - Smallpox vaccine is effective 85% in monkeypox. However, smallpox vaccination is stopped in most parts of the world in the late 1970s resulting in no or very little immunity in people born after the late 1970s.
  - The Centers for Disease Control and Prevention recommends smallpox vaccine for high-risk individuals. Does not recommend preexposure vaccination for other individuals.
  - General precautions such as personal protective equipment are recommended before caring infected person.

FIGURE 6.8 Monkeypox. *Source: CDC (PHIL).*

6.6 Enterovirus

This group belongs to Picornaviruses family. These viruses infect intestinal epithelial cells and lymphoid such as tonsils and Peyer's patch. They spread via fecal–oral route and respiratory secretions.

- Poliovirus
- Coxsackie A and B Virus
- Echovirus

6.6.1 Poliovirus

- Single-stranded, positive-sense RNA virus belongs to a family of Picornaviridae.
- Transmission is fecal–oral route and rarely with the respiratory droplets.
- Rare cases of oral vaccine related polio have been reported.
- Virus has three serotypes 1, 2, and 3. Type 1 is most likely involved in paralytic infection.
- Causes polio.

6.6.1.1 Polio

- Signs and symptoms:
  - Most of the patients are asymptomatic or have a mild febrile illness or may develop aseptic meningitis without paralysis.
  - Initial symptoms are flu-like lasting 2–5 days.
  - About 1% or less develop asymmetrical limb paralytic poliomyelitis, which is a flaccid paralysis without losing sensory sense.
  - The virus infects motor neurons in the anterior horn of the spinal cord.
  - Patient develops lower motor neuron lesion such as flaccid paralysis, fasciculation, hyporeflexia, and muscles atrophy.
  - Some patients about 4% develop aseptic meningitis
- Risk factors:
  - Unvaccination
  - Poor sanitation
  - Endemic area
  - Age younger than 5 years
- Diagnosis
  - Clinical
  - Lumbar puncture
  - RT-PCR →sample obtain from cerebrospinal fluid (CSF).
  - Viral culture → using stool, throat swab, or CSF specimens.
  - Serological tests

- Treatment: Supportive
- Prevention → vaccine
  a) Live attenuated oral vaccine → Not available in the United States. Associated with rare cases of vaccine-related paralytic polio.
    - Should not be given to immune compromise patients.
  b) Inactivated formalin-killed virus vaccine given subcutaneously.

6.6.2 Coxsackie virus

- Single-stranded, positive sense, icosahedral capsid, naked, mRNA virus.
- Coxsackie virus has several serotypes. Broadly classified into groups A and B. Group A is further classified into serogroup A1 to 21 and 24. Group B to B1–B6. They all can cause the following:
  - Cold
  - Febrile illness
  - Rashes
  - Aseptic meningitis
  - Sepsis in neonates
- Coxsackie A virus: responsible for:

6.6.2.1 Herpangina

- Fever, sore throat, and small red vesicles at the base of the throat.
- Other symptoms are fussiness, poor feeding, anorexia, headache, and encephalitis.
- Associated with serotype B and serotype A16 and enterovirus 71 serotypes.
- Usually infects young children younger than 10 years old.
- Worldwide
- Serotype A16 causes hand-foot-mouth disease. A25 causes hemorrhagic conjunctivitis and A7 causes permanent paralysis, which is rare.

6.6.2.2 Hand-foot-mouth disease

- Characterized by blister or sores in the mouth, rash or blister on the hands and feet.
- Other symptoms are fever, sore throat, irritability, headache, malaise, and decreased appetite.
- Usually infects children under the age of five or children in daycare.
- Transmission is fecal–oral and respiratory droplets.
- Self-limiting and goes away in 7–10 days with supportive treatment.

- Coxsackie B virus:
  - Infect visceral organs → gastroenteritis, pericarditis, myocarditis, encephalitis
  - Pleurodynia: Fever, headache, and pleuritic chest pain that worsens with breathing. May be confused with myocardial infarction and may last 2 days to 2 weeks.

  - Encephalitis and aseptic meningitis.
  - Pancreatitis
- Risk factors:
  - Warm and tropical climates.
  - Close contact with the infected person.
  - Poor hygiene and hand washing practices.
  - Low socioeconomic status.
- Treatment:
  - Nonsteroidal antiinflammatory drug (NSAID), supportive

6.6.3 Echovirus

- Group of viruses that mostly belong to a family of Picornaviridae.
- Associated with cold, rash, influenza-like symptoms, viral meningitis, and pericarditis
- Treatment is supportive

6.7 Hepatitis

Inflammation of liver cells

Main causes

- Viruses
- Alcohol
- Fatty liver disease
- Drugs, e.g., isoniazid

6.7.1 Classification

a) acute
b) chronic
c) fulminating

6.7.2 Acute hepatitis

- Less than 6 months
- Three phases
  - Preicteric phase → patient feels anorexic, malaise with nausea, vomiting, and may have upper right quadrant pain.
  - Icteric phase: patients develop jaundice, and the liver is usually tender and enlarged.
  - Recovery phase: jaundice subsides, and patient feels better.

- All hepatitis viruses cause acute hepatitis except hepatitis C, which causes very mild symptoms, and the patient usually does not develop jaundice.
- Alanine transaminase (ALT) and aspartate transferase (AST) are many times higher than normal values. In viral hepatitis, ALT is usually higher than AST.
- Alkaline phosphatase and bilirubin are mildly elevated.

6.7.3 Chronic hepatitis (Fig. 6.9)

- Asymptomatic to mild symptom
- Greater than 6 months
- Low-grade fever, malaise, fatigue ± upper abdominal pain. Jaundice might be absent.
- Liver enzymes mildly elevated.
- Major complications → cirrhosis, hepatocarcinoma
- Hepatitis B and C viruses commonly associated with chronic hepatitis.

6.7.4 Fulminating hepatitis

- Rapid deterioration of the liver results in liver necrosis. Hepatitis B virus ± hepatitis D virus as coinfection is the most common cause, but other viruses, drugs, and alcohol are also associated with fulminating hepatitis.

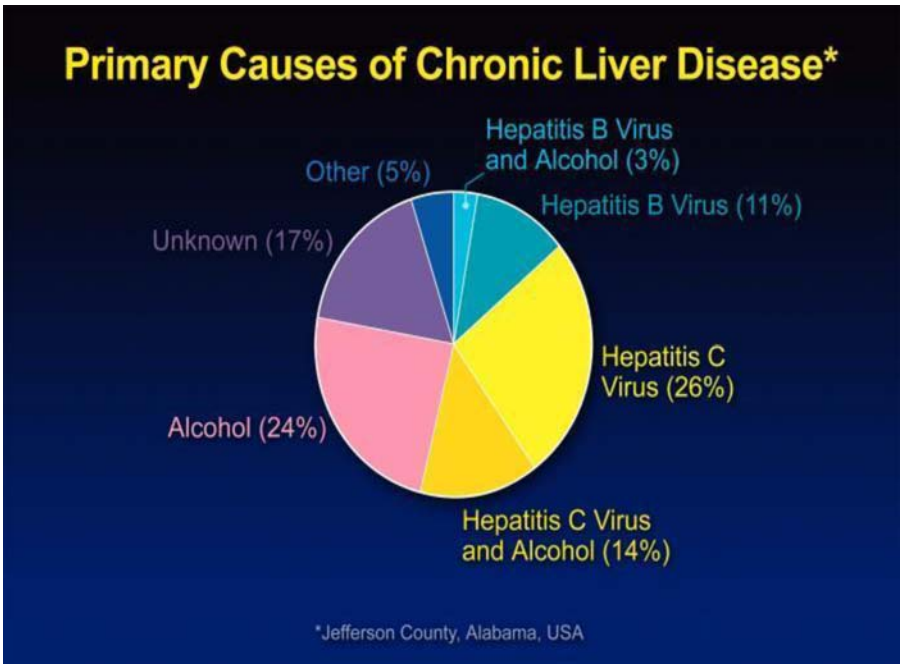

Primary Causes of Chronic Liver Disease*
Hepatitis B Virus and Alcohol (3%)
Other (5%)
Hepatitis B Virus (11%)
Unknown (17%)
Hepatitis C Virus (26%)
Alcohol (24%)
Hepatitis C Virus and Alcohol (14%)
*Jefferson County, Alabama, USA

FIGURE 6.9 Causes of chronic liver disease. *Source: CDC/Jefferson county Alabama.*

Hepatitis viruses:

1) Hepatitis A
2) Hepatitis B
3) Hepatitis C
4) Hepatitis D
5) Hepatitis E
   - All hepatitis viruses are RNA viruses except hepatitis B virus, which is a DNA virus
   - Hepatitis A and E spread via oral–fecal route. All others mentioned above are spread via blood, body fluids, and needle

6.7.5 Hepatitis A virus

- Worldwide, especially in developing countries
- Infects 1.5 million people worldwide each year.
- Single-stranded, nonenveloped, positive-sense mRNA virus that belongs to a family of Picornavirus.
- Transmission is fecal–oral route.
- Tropism: Liver cells
- Most common cause of acute hepatitis
- Does not cause chronic hepatitis
- Most children are asymptomatic, while adults usually develop symptoms of acute hepatitis.
- Signs and symptoms:
  - Incubation period 15–45 days
  - Initial symptoms are nonspecific such as fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, and headache.
  - Icteric phase: lasting 1–3 weeks, signs of liver damage such as jaundice, dark urine, and stool and increased liver enzymes (ALT rises more than AST).
  - Illness usually lasts 2–4 weeks, and patients fully recover.
- Serology:
  - Anti-HAV. IgM → acute infection
  - Anti-HAV. IgG → previous infection → protective and acquired immunity.
- Risk factors:
  - Poor hygiene as it spreads via fecal–oral route
  - Developing countries with poor sanitation
  - Drinking contaminated water or eating food contaminated by infected food handlers
  - Men to men sex
  - Contact with an infected person
- Treatment: Supportive
- Vaccine:

  - Children: 2 doses → first dose at the age of 12–23 months and second dose is at 6–18 months after the first dose.
  - Adults: 2 doses → 0 and 6–12 months after the first dose
- Postexposure:
  - Vaccine if unvaccinated
  - Immunocompromised → immune globulin.

6.7.6 Hepatitis B virus (HBV)

- DNA, double-stranded, enveloped virus, which belongs to a family of Hepadnavirus.
- Causes both acute and chronic hepatitis. May also cause fulminating hepatitis which has the worst prognosis.
- 90% of infected infants with acute hepatitis B will develop chronic hep-B, while 5% of infected adults will develop chronic hep-B.
- Several genotypes A-J have been identified and found in various regions of the world. Genotyping plays an important role in liver disease progression and response to interferon therapy.
- Structure of hepatitis B virus (Fig. 6.10):
  - Double-stranded DNA with DNA polymerase surrounded by icosahedral capsid called core antigen (HBcAg).
  - Surrounding the capsid is enveloped with a surface antigen called hepatitis B surface antigen (HBsAg).
  - During active infection, soluble component of viral core is released and called hepatitis cleavage antigen (HBeAg).
- Serology:
  HBsAg → Active infection
  Anti-HBsAg → immunity or no active disease or vaccinated.
  Anti-HBcAg (IgM) → new infection
  Anti-HBcAg (IgG) → old infection
  Antibodies against HBcAg are not protective
  HBeAg → high infectivity
  Anti-HBeAg → low infectivity
- Risk factors (Fig. 6.11):
  - Infants born of infected mothers
  - IV drug user
  - High-risk sexual behaviors
  - History of incarnation
- Treatment:
  - Supportive → about 95% immunocompetent patients develop antibodies to hepatitis B surface antigen without any treatment

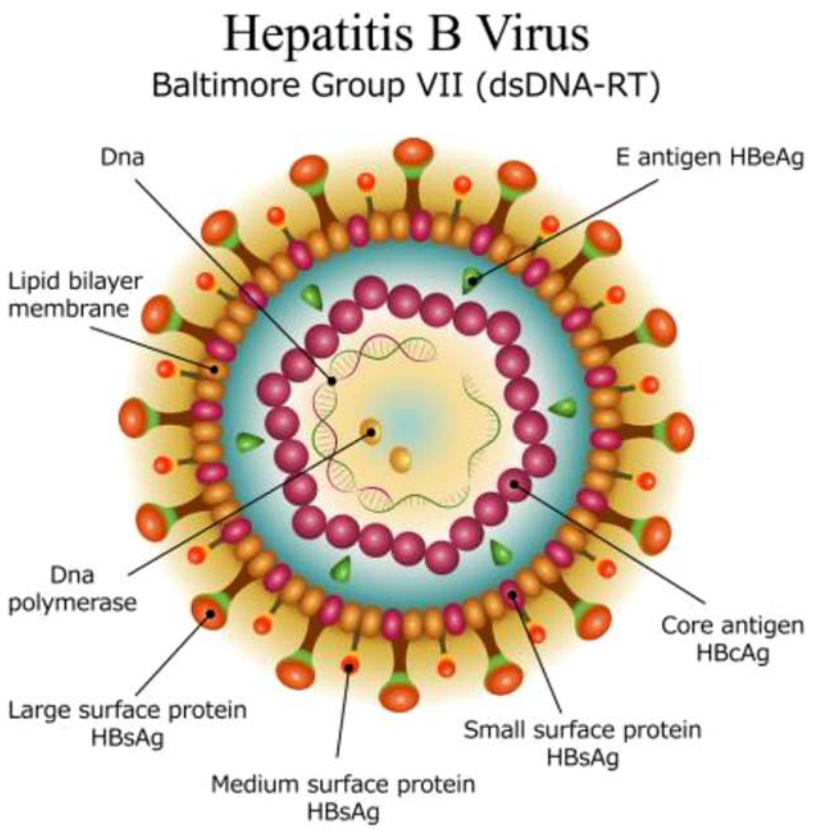


FIGURE 6.10 Hepatitis B virus.

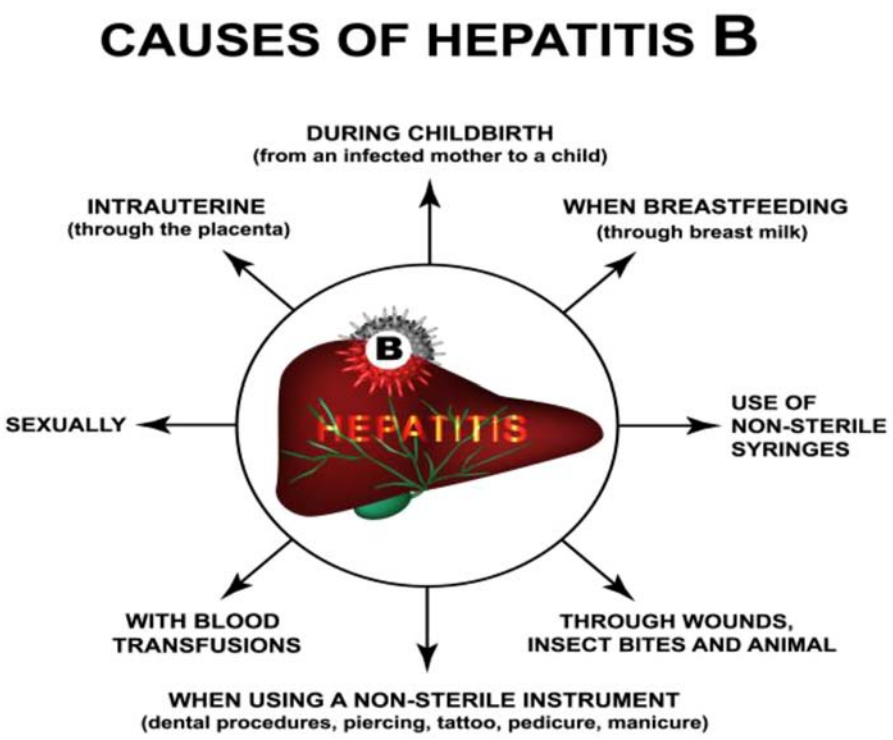


FIGURE 6.11 Causes of hepatitis B.

  - Oral nucleoside or nucleotide analogs such as entecavir, tenofovir disoproxil, or tenofovir alafenamide ± pegylated interferon alpha
  - Pregnant women → tenofovir disoproxil or lamivudine
  - Liver transplant
- Extrahepatic Manifestations:
  - Membranous glomerulonephritis is the extra liver manifestation of hep-B and hep-C viruses.
  - Serum sickness–like syndrome
  - Polyarteritis nodosa
- Vaccine: Series of three injections on 0, 1, and 6 months apart.

6.7.7 Hepatitis C virus (HCV)

- RNA single-stranded, positive sense virus, which belongs to the flavivirus family
- Mostly results in chronic hepatitis
- 20%–30% of patients develop cirrhosis
- Genotypes 1, 2, 3, 4, 5, and 6 exist in various parts of the world.
- Genotypes 1, 2 present in the United States of America
- Risk factors:
  - IV drug users or any other work which requires skin puncture or bleeding
  - Blood transfusion before 1992 or organ transplants recipients
  - HIV infection
  - Unsafe medical practice
  - Incarceration → prevalence is higher in inmates
  - Fetus of an infected mother; vertical transmission risk is 2.4% which increases with high viral loads or if the mother is coinfected with HIV
- Diagnosis:
  - Serology
  - PCR
  - Liver biopsy is a gold standard for staging hepatitis C virus (HCV) infection or liver fibrosis but is rarely used due to availability of noninvasive fibroscan or elastography.
- Complications: Cirrhosis, hepatocarcinoma (Fig. 6.12)
- Extrahepatic manifestations:
  - Cryoglobulinemia
  - Porphyria cutanea tarde
  - Glomerulonephritis
- Treatment: (see Section 6.15.2)
  - Most of the treatments involved combinations:
    - Protease inhibitor "——previr"
    - NS5a inhibitors "————asvir"
    - Nucleoside/Nonnucleoside (NS5b) inhibitor "————buvir"
  - Examples are: sofosbuvir + ledipasvir, sofosbuvir + velpatasvir, elbasvir + grazoprevir.

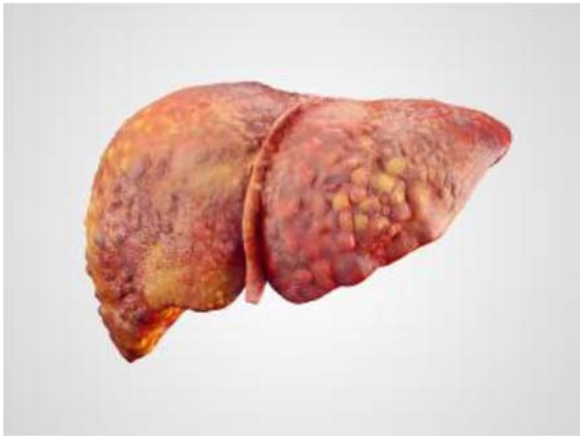


FIGURE 6.12 Cirrhosis.

6.7.8 Hepatitis D virus (HDV)

- Defective RNA virus that cannot replicate itself
- Requires hepatitis B virus (HBV) for infection
- Two ways to infect:
  - Coinfection: Both hepatitis B virus (HBV) and hepatitis D virus (HDV) are transmitted at the same time. Antibodies to HBsAg are protective for both infection
  - Superinfection: Patient already has chronic Hep-B, and HDV infects the patient. It may result in acute to fulminating hepatitis, which has the worst prognosis.
- Diagnosis:
  - Serology → Hep-D antibody test.
  - PCR
- Treatment:
  - Supportive
  - Alpha interferon-2b
  - Vaccine not available. HBV vaccination provides protection against HDV also.
  - Liver transplant

6.7.9 Hepatitis E virus

- Single-stranded, positive-sense RNA virus that belongs to a family of Hepeviridae.
- Has serogroups A–D. Group A infects human, pigs, deer, and rabbits. Group B infects rodents and avian. Group D infects bats.
- Spreads via fecal–oral route, contaminated food, and water supply. Causes infection worldwide, mostly unhygienic area and underdeveloped countries.
- Usually results in acute hepatitis with no chronic hepatitis
- Infection in pregnant women can result in fulmination hepatitis

- Diagnosis:
  - Serology → Hep E IgM and IgG antibodies.
  - PCR
- Treatment:
  - Supportive
  - Ribavirin in immunocompromised patients.
  - Vaccine is available in China

6.8 Viruses infect CNS

6.8.1 Rabies virus

- RNA single-stranded, negative-sense, bullet-shaped virus with a helical shape capsid and belongs to a family of rhabdoviruses.
- Tropism: neural tissue.
- Rabies virus causes viral encephalitis (rabies), transmitted from the saliva of infected mammals such as dogs, bats, raccoons, skunks, and foxes.
- Virus uses nicotinic acetylcholine receptor to enter into muscle cells in the area of the bite and reaches to the neuromuscular junction, from where it enters into motor neurons. The virus replicates in motor neurons and moves slowly in a retrograde direction, reaches to the central nervous system, and infects brain and other structures.
- Usual incubation time is 1–2 months but may take up to a year
- Signs and symptoms:
  - Initial symptoms are fever, headache, malaise, paresthesia, or tingling or burning at the site of infection. Clinical phase is divided into two types:
  - **Encephalic or furious type**: Fever, headache, restlessness, confusion, agitation, abnormal behavior, excess salivation, drinking causes painful pharyngeal/laryngeal muscles spasm (hydrophobia), aerophobia, slurred speech, and dysphagia.
  - **Paralytic type**: About 20 of percent patients developed ascending paralysis without delirium and hydrophobia.
  - Both forms lead to coma and death secondary to cardiopulmonary failure.
- Diagnosis:
  - Clinical
  - Skin biopsy → Fluorescent
    Antibody testing for rabies
    Specific antibodies.
  - PCR
  - Serology
  - CT, MRI → not a diagnostic

Animals infected with rabies usually show strange behavior. They do not show any fear of human. Nocturnal animal comes in daytime and makes strange noises and cannot fly

- Treatment
  - Supportive, once symptoms appear nothing can be done.
  - Heavy sedation once symptoms have started
  - Do not give immune globulin or vaccine once symptoms start. May cause rapid deterioration of the patient condition.
- Vaccine:
  - Available for high-risk people
  - Total of three doses are given at 0, 7, and 21−28 days
- Postexposure:
  - Thoroughly clean the wound with soap and water
  - Infiltrate immune globulin (20 units/kg) around the wound and give rest IM.
  - Vaccine on days 0, 3, 7, and 14. Give vaccine on limb other than the one used for immune globulin.
  - Start immediate vaccination and immune globulin if the bite involved bats, raccoons, skunks, foxes, and other carnivores
  - Domestic dogs, cats, and ferrets → observe the animal for 10 days. Do not start prophylaxis until the animal shows any sign of rabies
  - Stray dogs, cats, and other rodents with a high probability of rabies → start immune globulin prophylaxis immediately.

Infected CNS cells have inclusion bodies with full of viral proteins called Negri bodies

6.8.2 John Cunningham Virus (JC virus)

- JC virus is a double-stranded, closed circular DNA virus belonging to a family of papovaviridae.
- The virus is associated with progressive multifocal leukoencephalopathy (PML). As the name indicates, it is a white matter disease that affects multiple locations and worsens over time.
- Caused by reactivation of JC virus in immune-compromised patients (AIDS).
- Transmission: The virus is transmitted via the respiratory droplets or gastrointestinal (GI) tract and reaches the kidney, where it remains dormant in the epithelial cells of the kidney.
- Virus gets activated when the immune system gets weakened.

- The virus has a propensity for oligodendrocyte cells and causes demyelination of white matter of the central nervous system in multiple locations.
- Risk factors:
  - AIDS patients, especially when CD4 + T cells are less than 200 cells/ul.
  - Patients using immunomodulatory drugs
  - Organ transplants, multiple sclerosis, and other autoimmune disease patients who are on immune-suppressive drugs
  - The prevalence of PML in the general population is 0.22 per 100,000 individuals.
- Signs and symptoms:
  - Multifocal neurological deficit.
  - Symptoms depend on the location of lesions.
  - Hemiparesis, aphasia, dysarthria, hemianopia, cognitive impairment, clumsiness, and personality changes.
- Diagnosis:
  - MRI
  - CSF PCR → viral DNA
- Treatment:
  - Highly active antiretroviral therapy (HAART)
  - Supportive

6.9 Viruses causing meningitis/encephalitis

- Viruses that cause meningitis/encephalitis are as follows:

6.9.1 Enteroviruses

Coxsackievirus is the most common enterovirus virus responsible for encephalitis. It is mostly spread via fecal−oral route. Discussed in Section 6.6.2

6.9.2 Herpes simplex virus

Close contact. Discussed in Section 6.11.1

6.9.3 Varicella zoster virus

Inhalation droplets or close contact. Discussed in Section 6.11.2

Other viruses responsible for meningitis or CNS infection are given below.

6.9.4 Arbovirus

- These viruses are called arbovirus because they are transmitted to humans by blood sucking arthropods such as mosquitoes and ticks. The mosquito or tick becomes infected when fed on the blood of infected animals. The virus replicates in

mosquitoes or tick's stomachs and reaches the salivary glands. A human is infected when these mosquitos or ticks bite. These viruses belong to various families, such as Togaviridae, Flaviviridae, Bunyaviridae, and Reoviridae.

- Alphavirus is one of the genera of the family Togaviridae. There are 27 alphaviruses classified on the basis of antigenic properties. Few cause infections in humans.
- Flavivirus: One of the genera of the family Flaviviridae causes encephalitis or hemorrhagic fever in humans.

6.9.5 Mosquito-borne

6.9.5.1 Togaviridae family

- Several species of Togaviridae family are responsible for meningitis in humans. They are transmitted to humans from the mosquitoes Culex species. These viruses are positive-sense, single-stranded, with icosahedral symmetry, and enveloped RNA viruses. They include the following species:
  - **Western equine virus**: Infects human and horses. Mostly reported in the area of Western US and Canada
  - **Eastern equine virus**: Eastern US
  - **Venezuelan equine virus**: Southern US, and South, and Central America.

6.9.5.2 Bunyaviridae family

- **California encephalitis virus**: Single-stranded, negative-sense with helical symmetry, segmented RNA virus, belonging to a family of Bunyaviridae and transmitted to human by Aedes mosquitoes.
- **Signs and Symptoms**: Most of the infected patients are asymptomatic, but some may develop flu-like symptoms, and a few patients may develop severe disease such as encephalitis, meningitis, or flaccid paralysis.
- Diagnosis: Serological testing. Specific IgM antibodies in serum or CSF. Reverse transcriptase PCR and viral culture
- Treatment:
  - Supportive. No vaccine is available, prevention

6.9.5.3 Flavivirus: both, mosquito born and tick born

- **West Nile virus**: Positive-sense, single-stranded, enveloped RNA virus that belongs to a genus *Flavivirus* and the family of Flaviviridae. It usually infects many species of birds. The virus is transmitted from bird to human by the infected mosquito, or by blood transfusion, organ transplants, and from mother to fetus transplacentally.
- **Zika virus**:
  - Single-stranded, positive-sense, enveloped RNA virus that belongs to the family of Flaviviridae and genus *Flavivirus*.
  - Transmitted by the bite of female mosquito of species *Aedes aegypti* and *Aedes albopictus*.

- Zika virus can also be transmitted by:
  - Person to person → sexually contact
  - Blood transfusion
  - Organ transplantation
  - Maternal–fetal vertical transmission
- Majority of the people have mild and self-limited symptoms.
- Signs and symptoms:
  - Incubation period is 2–14 days
  - Fever
  - Rash → maculopapular
  - Joint pain
  - Conjunctivitis and retro-orbital pain
  - Cases of acute myelitis and meningoencephalitis have been reported.
- Pregnancy:
  - Infection during pregnancy is a major concern and is associated with the following:
    - ➢ Microencephaly and brain abnormalities in the fetus
    - ➢ Other congenital disabilities such as vision loss, hearing loss, and seizures.
- Diagnosis:
  - Clinical → History of exposure to the virus.
  - PCR
  - Antibodies
- Treatment:
  - Supportive
  - No vaccine

6.9.6 Ticks born

6.9.6.1 Flavivirus

- Three subtypes: European, Siberian, and the Far Eastern flavivirus.
- *Ixodes ricinus* tick in Europe and *Ixodes persulcatus* in Siberia and the Far East are responsible for transmitting the virus to humans.
- In the United States, the ***Powassan virus*** is also a flavivirus that is responsible for most cases, especially in Northeastern states and the Great lake region. The tick responsible for transferring the virus to humans is deer tick (*Ixodes scapularis*). This is the same tick responsible for Lyme disease. Other ticks, such as squirrel ticks and groundhog ticks, can also transmit the disease to humans.
- Virus can also be transmitted by ingesting unpasteurized dairy products, blood transfusion, organ transplants, and breastfeeding but not very common.

- **Colorado Tick fever virus**:
  - Belongs to a family of Reoviridae, double-stranded RNA virus with icosahedral capsid.
  - People are infected from the bite of an infected Rocky Mountain wood tick (*Dermacentor andersoni*).
  - Small rodents such as squirrels, chipmunks, and mice are the reservoir for the virus.
- **Signs and symptoms**: About 2/3 of patients remain asymptomatic. Most often symptoms are biphasic. After the incubation period, which ranges between 4 and 28 days, people develop fever, malaise, headache, nausea, and vomiting for 5–7 days and then 1 week of the symptom-free period. Some infected patients develop neurological symptoms such as meningitis, cranial nerve palsy, seizures, coma, and death.
- Diagnosis:
  - Specific IgM and IgG antibodies in patient serum and CSF
  - PCR
- Treatment:
  - There is no treatment
  - Supportive treatment

6.9.7 Chikungunya virus

- Not a very common cause of meningitis but should be considered in patients who traveled to endemic areas.
- Diagnosis:
  - CSF analysis, gram stain, and culture
  - PCR
- Treatment:
  - Supportive
  - Acyclovir IV → effective for HSV
  - HIV-associated meningitis: treat with anti-HIV drugs

6.10 Viruses causing hemorrhagic fever

6.10.1 Yellow fever virus

- Arbovirus, single-stranded, positive-sense, enveloped mRNA virus that belongs to the genus *Flavivirus* and the family of Flaviviridae.
- Causes yellow fever
- *Haemagogus* mosquito transmits the virus among monkeys in the jungle, and from monkeys, it is transmitted to humans and is called Sylvatic or Jungle yellow fever.
- In urban area, the virus is transmitted by the bite of the mosquito *A. aegypti* and is called urban yellow fever.
- Endemic in South America and Sub-Saharan Africa

- Once inside the human, the virus infects dendritic cells and travels to lymphatic vessels. From lymphatic vessels, it reaches the bloodstream and infects various organs such as liver, kidneys, heart, and GI tract.
- Sign and symptoms:
  - Incubation period 3–5 days.
  - Sudden onset of fever
  - Headache
  - Myalgia
  - Jaundice, hepatitis
  - Decrease heart rate or bradycardia
  - In mild disease, symptoms resolve in in 2–3 days. However, in moderate to severe disease, fever comes back and shows sign of disseminated infections such as jaundice, hepatitis, albuminuria, oliguria, hematemesis, mucosal hemorrhage, myocardial infarction, seizure, coma, multiorgan failure, and death.
- Diagnosis:
  - Viral culture
  - RT-PCR
  - Serology
  - Clinical symptoms and recent travel history to endemic area.
- Treatment:
  - Supportive
  - Vit K and H_2 blocker prophylaxis for GI bleeding
  - Vaccination: Live attenuated vaccine is available for high-risk patients. Contraindicated for pregnant women, infant <6 month, and immunocompromised person. It is also contraindicated for people who are allergic to eggs, gelatin, or chicken protein.
  - Quarantine the patient.
  - Avoid using aspirin or NSAID as it increases the chances of bleeding.

6.10.2 Dengue fever virus

- Flavivirus, arbovirus, single-stranded, positive-sense, enveloped virus that belongs to a family of Flaviviridae.
- Transmitted from the bite of a female *Aedes* mosquito.
- Primary reservoirs are humans and mosquitoes.
- Endemic in Southeast Asia, Caribbean island, Porta-Rico, and US Virgin Island.
- Dengue or breakbone fever is caused by four closely related serotype viruses named Den-1, Den-2, Den-3, and Den-4. They share about 65% of their genome. Infection of one serotype does not provide long-term protection from the other strain. After a short period of time, the person can be infected with any other strain and subsequent infection usually results in severe dengue illness.
- Pathophysiology of dengue fever resulting in severe symptoms is poorly understood. The common census is that multiple factors, including prior immunity, viral load, viral proteins NS1, and anti-NS1 antibodies, serotype, and genotype, may

contribute to the severity of the disease. However, it is suggested that viral nonstructural protein NS1 plays an important role in the severity of the disease. NS1 protein is involved in disrupting the integrity of the endothelial cells and elicits inflammatory cytokines, activating macrophages and the compliment system. This results in increased endothelial permeability, coagulopathy, and thrombocytopenia.

- Signs and symptoms:
  - Incubation period is 4–7 days. Symptoms range from asymptomatic and moderate febrile illness to serious manifestations such as dengue hemorrhagic fever and dengue shock syndrome, especially in secondary dengue cases.
  - Sudden onset of high fever, headache, eye movement that causes retro orbital pain, myalgias, back pain, arthralgias and generalized lymphadenopathy, brief period of afebrile days and then rise of temperature again followed by a blanching rash, ± cough, sore throat and rhinorrhea, and nausea vomiting. Mild cases usually remit in 72 h, but severe cases may last up to 1 week. Some patients may develop dengue hemorrhagic fever, which results in an increased tendency to bleed, thrombocytopenia, and shock. Few patients may develop Guillain–Barre syndrome.
- Diagnosis:
  - Serologic test and antigen test
  - PCR
  - Complete blood count → shows leukopenia and thrombocytopenia
  - Coagulation test,
  - Liver test
  - Urinalysis
- Treatment:
  - Supportive
  - No antiviral works
  - Do not use NSAID as it increases the risk of bleeding.
  - Vaccine: Tetravalent vaccine was evaluated in Mexico and Philippines. The vaccine decreases the risk of hospitalization and severe disease in seropositive patients. However, vaccinating seronegative children increases the risk of severe disease if they are infected with the dengue virus later. This halted the vaccination and now it is recommended for seropositive patients only. Three doses of vaccine are given 6 months apart.
- Dengue hemorrhagic fever/shock syndrome:
  - Primarily requires prior exposure to dengue virus.
  - Overacting proinflammatory response to the virus results in shock syndrome.
  - Warning sign:
    - Marked change in temperature → fever to hypothermia
    - Severe abdominal pain

  - Persistent vomiting and hematemesis
  - Lethargy, confusion.
  - Black stool, bleeding from gums or any other signs of bleeding.
- World Health Organization criteria for diagnosis:
  - High fever for 2−7 days
  - Hemorrhagic manifestations
  - Hepatomegaly
  - Thrombocytopenia <100,000 plt/mcL
  - ↑prothrombin time
  - ↑activated partial thromboplastin time (PTT)
  - ↓fibrinogen
  - ↑D-dimers

6.10.3 Marburg and Ebola virus

- Single-stranded, negative-sense RNA viruses that belong to a family of Flaviviridae
- Cause acute hemorrhagic fever
- Both viruses cause clinically similar infections. However, the infection caused by the Ebola virus is more virulent.
- Most of the cases are reported in Central and West Africa. However, isolated cases have been reported in the United States of America and Europe.
- Exposure to nonhuman primates transmits the virus to human
- Human-to-human transmission can occur via skin or mucous membrane contact and body fluids
- Symptoms start with fever, myalgia, headache, and abdominal pain with vomiting and diarrhea. After a few days, hemorrhagic symptoms start with petechiae, ecchymoses, and bleeding from the mucous membrane and any punctured site.
- Patient developed hypovolemic shock and multiorgan failure; fatality could range from 25% to 90%
- Ebola virus can survive in the CNS, and relapse could happen
- Diagnosis:
  - Clinical
  - ELISA
  - RT-PCR
  - Report to public health authority and follow their advice
- Treatment:
  - Immediate isolation of the patient and strict control to protect others
  - Supportive treatment
  - Monoclonal antibodies REGN-EB3 and mab-114
- Vaccine: available in a high-risk area

Ebola virus persist in semen for long time. It is advised not to do sex for at least 12 months or 2 negative tests.

6.10.4 Hantavirus

- Hantavirus is a single-stranded, enveloped, negative-sense, circular RNA virus belonging to a family of Bunyaviridae and has nine viruses in the group. All cause similar infection.
- Present all over the world
- Rodents are the carriers and shed the virus in the urine and feces.
- Transmission to humans is via inhalation or bite of a rodent (rare), or contact with rodent urine, saliva, or feces.
- Associated with the following:
  - Hemorrhagic fever with renal syndrome
  - Hantavirus pulmonary syndrome

6.10.4.1 Hemorrhagic fever with renal syndrome

- Incubation period is 2–4 weeks
- Symptoms begin with flu, high fever, headache, back pain, abdominal pain, and vomiting. The fever lasts 3–7 days and ends with conjunctival hemorrhages and palatal petechiae. The illness quickly progresses to bleeding, oliguria, renal failure, and shock. Some patients develop seizures or focal neurological symptoms. Fatality is 6%–15%. Oliguria phase lasts 3–7 days, and then kidney function starts improving and full recovery in 6–7 months without significant long-term complications.

6.10.4.2 Hantavirus pulmonary syndrome

- Starts with the prodromal phase with a flu-like symptoms. Nausea, vomiting, thrombocytopenia, and dyspnea without cough. Absence of cough distinguishes HPS from pneumonia or ARDS. This phase usually lasts about 2–3 days. In severe disease, symptoms quickly deteriorate and progress to pulmonary edema, hypoxemia, hypotension, and acute respiratory failure. Patients at this phase may develop kidney failure and cardiogenic shock. Mortality rate is 50%–70%.
- Diagnosis:
  - Serological test
  - PCR
  - Immunofluorescent or immunoblot assay. ELISA
  - Complete blood count → Thrombocytopenia, presence of immunoblasts, atypical lymphocytes, ↑HCT
  - Coagulation tests → ↑aPTT,

- Urine analysis
- Renal function tests
- Chest X-ray → bilateral pulmonary edema

- Treatment:
  - Ribavirin → shows some benefits.
  - Dialysis
  - Supportive care

6.11 Viruses infecting skin or mucus membrane

6.11.1 Herpes simplex virus 1 and 2

- Double-stranded, enveloped DNA virus that belongs to a family of Herpesviridae.
- There are two types of herpes simplex virus (HSV)—HSV1 and HSV2. HSV1 usually causes infection above the waist and HSV2 below the waist. However, there is a significant crossover.
- The virus initially replicates in epithelial cells producing characteristic vesicles. It then ascends to the sensory nerve to the dorsal root ganglia.
- HSV remained dormant in dorsal root ganglion of sensory neurons and repeatedly reemerged to cause painful symptoms.
- Transmission by close contact. Considered sexually transmitted disease.
- Prodrome: tingling sensation usually a few hours or days before the appearance of clusters of small, painful, fluid filled blisters that oozes and ulcerate. Healing usually occurs 10–20 days or 5–10 days in recurrent infection.
- Usual sites of infection are:
  Herpes labialis: at the vermillion border of lip (cold sore) (Fig. 6.13)
  Genital herpes: at the site on the penis, vulva, cervix, and labia
  Herpetic whitlow: lesion at the finger
  Eye: keratoconjunctivitis
  - Most common cause of corneal blindness
  - Characteristic branching or dendritic ulcer can be seen on eye examination.
  - Pain, redness, and tearing
  - Sensitivity to light

- Common cause of sporadic meningitis and encephalitis, typically affecting the temporal lobe.
- Neonatal herpes is transmitted during vaginal birth if the mother has active genital lesions. Cesarean section is recommended. Give acyclovir starting 36 weeks of gestation.
- Infection in neonates has three stages:
  1) Skin, eye, and mucus membrane infection
  2) CNS infection
  3) Disseminated infection → septic shock

- Diagnosis:
  - Tzanck smear → preparation is stained to identify multinucleated giant cells of HSV
  - PCR
  - Serology test or antibody test
  - Culture
  - Immunofluorescence staining
  - MRI
- Treatment:
  - Acyclovir
  - Famciclovir
  - Valacyclovir
  - Penciclovir
  - Docosanol → Abreva for cold sore
- Vaccine: Not available

6.11.2 Varicella-zoster virus (human herpesvirus type 3)

- Double-stranded DNA virus belonging to a family of Herpesviradae.
- Chicken pox is the primary infection of varicella-zoster virus, while shingle is the reactivation of the virus
- Once the virus infects humans, it lies dormant in the dorsal root ganglia and is reactivated as cell-mediated immunity decreases.
- Caused chickenpox and shingle.

FIGURE 6.13 Cold sore.

6.11.2.1 Chickenpox (Fig. 6.14)

- Primary infection usually infects children.
- Symptoms start with mild fever, headache, and malaise followed by macular rashes, which convert to maculopapular rashes with intense itching.
- Rash starts on the trunk and spreads to the face and extremities
- Lesions develop in crops and are in various stages of development. Lesions crust in 2–5 days.
- Complete clearance takes about 15–20 days.
  - Transmission:
    - Respiratory secretion
    - Touching the lesion
    - Infective period: 2 days before the start of rash till lesion crust
  - Complication:
    - Children usually have mild course, but in adult and immunocompromised patients, it could be fatal.
    - Infants exposed to the virus during the first 10 days of life are at risk of developing neonatal varicella, which has a mortality rate of 30%. The exposed neonate can be given VZ immune globulin. And if symptoms appear, it should be treated with acyclovir.
    - Secondary bacterial infection.
  - Treatment:
    - Children 2–12 years old
      - No treatment is needed for mild to moderate disease
      - Valacyclovir or acyclovir for severe disease
    - Adolescents and adults:
      - Acyclovir, valacyclovir, and famciclovir

FIGURE 6.14 Chicken pox.

6.11.2.2 Shingles

- Reactivation of infection caused by varicella-zoster virus
- Lesions develop in crops, unilateral, very painful, with erythematous base, appear on the affected dermatomes of thoracic or lumbar region (Fig. 6.15).
- Symptoms usually last up to 4 weeks.
- Herpes zoster optics or Ramsay Hunt syndrome:
  - Infection of the geniculate ganglion results in pain in the ear, facial paralysis, and ± vertigo. Vesicles appear in the external auditory canal, and taste is lost in 2/3 of the tongue.
- Ophthalmic herpes zoster:
  - Involvement of Gasserian ganglion.
  - Pain and vesicle around the eye and forehead, V1 distribution of trigeminal nerve
  - Can cause conjunctivitis, anterior uveitis, glaucoma, and corneal scarring
  - Nasocillary nerve, a branch of the ophthalmic nerve (V1 branch of the trigeminal nerve). Vesicles on the nose are a sign (Hutchinson's sign) that ophthalmic nerve is infected and is indicated that the cornea is involved
  - Postherpetic neuralgia
    - Persistent or recurrent pain in involved dermatome
- Diagnosis:
  - Clinical
  - Tzanck test → multinucleated giant cell
  - Culture
  - PCR
  - Antigen test

FIGURE 6.15 Shingle.

- Treatment:
  - Acyclovir, valacyclovir, or famciclovir. Start within 24 h of the onset of rash
  - Vaccine: patient over 50 years of age
  - For eye involvement, topical corticosteroid + IV acyclovir

6.11.3 Human papilloma virus

- Double-stranded, circular, nonenveloped, DNA virus that belongs to a family of Papillomaviridae
- More than 100 subtypes
- Responsible for the following diseases in humans:
  - Common wart (Fig. 6.16)
  - Genital wart
  - Cervical Cancer
  - Anogenital cancer
  - Oropharyngeal cancer
- Virus enters the epithelium cells through disruption of skin or mucosa and infects basal stem cells where it replicates. Viral DNA carries genes called E6 and E7. The product (protein) of these genes interferes with the p53 and pRB gene of the host cell. This results in uncontrolled replication of epithelial cells and causes hyperplasia and wart formation.
- Common warts are benign, epidermal lesions that can appear anywhere on the body. Most of them are asymptomatic but may cause pain if located in weight-bearing area.
- Most warts resolve themselves but can be removed by using topical irritants like salicylic acid, cantharidin, or podophyllum resin.

FIGURE 6.16 Wart.

- Cryosurgery, electrocautery, curettage, excision, or laser treatment can be used.
- Genital warts (condyloma acuminatum) are benign anogenital warts caused by human papilloma virus (HPV) types 6 and 11
- HPV subtypes 16 and 18 cause 70% of cases of cervical cancer and cancer in other areas such as the penis, vulva, vagina, and oropharynx.
- Other subtypes 31, 33, 35, and 39 are responsible for the rest of cervical cancer.
- Diagnosis
  - Clinical
  - Biopsy
  - NAAT

HPV causes almost all cases of cervical cancer

- Treatment
  - Mechanical removal
  - Cryotherapy, electrocauterization, laser, and surgical removal
  - Topical applications
    - Podophyllotoxin, 5-fluorouracil, imiquimod
- Vaccine: available:
  - 9 − valent vaccine → protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58
  - Quadrivalent vaccine → protects against HPV types 6, 11, 16, and 18
  - Bivalent vaccine → protects against HPV types 16 and 18
- Schedule:
  - For both males and females, HPV vaccine is recommended at the age of 11 or 12 through 26 years of age.

6.12 Other herpes viruses

These DNA viruses belong to the family of Herpesviridae and cause various infections in humans:

- Epstein−Barr virus (HHV-4)
- Cytomegalovirus (HHV-5)
- Human herpesvirus 8 (HHV-8)

6.12.1 Epstein–Barr virus (HHV-4)

- Double-stranded DNA enveloped virus that belongs to a family of Herpesviridae.
- Transmitted by respiratory secretion or saliva containing the virus, such as sharing foods or drinks or kissing. Transmission has also occurred through organ transplantation and blood transfusion.
- Worldwide, over 90% population has been infected. In the United States, about 83% of adolescent population is affected.
- Virus usually infects two types of cells:
  - Oropharynx epithelial cells
  - B-cells
- In the mouth, the virus infects epithelial cells. Inside the epithelial cells, virus undergoes lytic cycle, produces viral proteins, and destroys the host cells.
- In B-cell, the virus enters the latent phase without destroying the B-cell and spreads the infection to other parts of the body.
- Most of the infection is asymptomatic but may be associated with:

CMV and toxoplasmosis both cause mononucleosis.
In CMV, there is atypical lymphocytosis, hepatitis, and less sever pharyngitis.
In toxoplasmosis, there is usually no pharyngitis.

6.12.1.1 Mononucleosis

- Epstein Barr Varius (EBV) or Human Herpesvirus-4 (HHV-4) is the most common cause of
  Mononucleosis.
- Signs and symptoms:
  - Fever
    - ➢ Sore throat (pharyngitis). Exudate may present.
    - ➢ Fatigue that may last for weeks
    - ➢ Lymphadenopathy
    - ➢ Splenomegaly
- Complications:
  - Encephalitis
  - Splenic rupture
  - Airway obstruction
  - Hemolytic anemia
  - Thrombocytopenia
  - Jaundice
  - Burkitt lymphoma
  - Nasopharyngeal carcinoma

  - Oral hairy leukoplakia in HIV-infected patients
- Diagnosis:
  - Peripheral blood smear shows the presence of atypical lymphocytes. Mostly cytotoxic CD8+ T cells.
  - Heterophile antibody test → Not very sensitive for children <5 years old. Heterophile antibodies are made by infected B-cells and react with antigen present on sheep or horse red blood cell causing agglutination.
  - EBV serology test → highly sensitive
- Treatment
  - Supportive
  - Corticosteroids
  - If a patient is given ampicillin or amoxicillin due to misdiagnosis he/she may develop maculopapular itchy rash which is not an allergic reaction. Reason for the rash is not known.
- Burkitt lymphoma→ Virus survives inside the B-cells, which results in the expression of viral gene, production of viral protein, and B-cell proliferation, leading to B-cell cancers such as Burkitt Lymphoma.
- Occasionally, EBV virus in oropharynx epithelial cells enters the latent phase, and instead of destroying the host cells, it stimulates the proliferation of the cells which may result in nasopharyngeal carcinoma.

6.12.2 Cytomegalovirus (HHV-5)

- Double-stranded, enveloped DNA virus that belongs to a family of Herpesviridae.
- Present worldwide, and it is estimated that about 60%−70% of adults are infected. Most infections in immunocompetent people remain asymptomatic but can be life threatening in an immune-compromised patient.
  - Latent infection persists throughout the life and is reactivated in case of decreased immunity.
  - Virus mostly replicates in the salivary gland and kidney and is shed in the saliva and urine.
  - Transmission is via body fluid such as saliva, blood, breast milk, urine, genital secretion, or organ transplant.
  - In primary infection, the virus infects epithelial cells and induces characteristic giant cells with intranuclear inclusions surrounded by a clear halo that looks like an owl's eye appearance.
  - The virus also infects monocytes and remains dormant and reactivated when the immune system weakens.
  - Cytomegalovirus (CMV) is associated with three clinical syndromes:
    - Primary infection CMV mononucleosis
    - Congenital CMV infection.
    - Infection in immunocompromised patients

- CMV mononucleosis:
  - Mostly affects immunocompetent people.
  - Symptoms are similar to mononucleosis caused by Epstein–Barr virus, except pharyngitis and cervical lymphadenopathy are rare or mild plus heterophile antibodies are negative.
  - Other symptoms such as anemia, hepatitis, thrombocytopenia, and other organ involvement are uncommon in immune-competent.
- Congenital CMV infection:
  - CMV is one of the most common viral infections that cause fetal defects and is grouped with other bacteria and viruses that cause birth defects and are listed under "TORCH."
  - The fetus gets infected if the mother is infected with primary CMV infection during pregnancy or reactivation. The rate of transmission from mother to fetus is about 5%.
  - The exact mechanism of how CMV causes birth defect in the fetus is unknown. However, CMV is cytopathic and responsible for cell damage. It also slows down cell division and causes inflammation of blood vessels which decreases the blood supply to the fetus.
  - These effects result in intrauterine growth restriction, oligohydramnios, or polyhydramnios.
  - Fetus born usually has petechiae, jaundice, hepatosplenomegaly, and microcephaly.
  - The baby may also have hearing loss or deafness and eye abnormalities and other developmental issues.
  - Congenital CMV can be diagnosed from amniotic fluid or fetal blood sample for viral culture or PCR. Ultrasound to detect fetus abnormalities can also be done.
  - Treatment for congenital CMV is to give ganciclovir or valganciclovir for 6 months. However, antiviral drugs do not reverse any damage that has already been done.

T = Toxoplasma
O = Others
R = Rubella
C = Cytomegalovirus
H = Herpes simplex virus

- CMV in immunocompromised patients:
  - Most common viral infection in the organ transplant patient.

- The risk of infection is greatest during 1−4 months after the organ transplant. Primary CMV causes more severe disease than reactivation in patients with organ transplant.
- Infects almost any organ. Transplanted organ is at particular risk.
- CMV also infects HIV patients whose CD4+ cell counts get below 50−100/uL.
- Sign and symptoms:
  - ➢ Fever, malaise, anorexia, fatigue, night sweating, and other symptoms depending upon the organ involved such as:
  - ➢ Retinitis → may result in blindness
  - ➢ Encephalitis
  - ➢ Pneumonia
  - ➢ Hepatitis
  - ➢ Colitis
  - ➢ Other disseminated diseases
- Diagnosis
  - ➢ Urine culture
  - ➢ CMV antigen
  - ➢ Serology tests
  - ➢ Biopsy
- Treatment
  - ➢ For serious infection → Ganciclovir, valganciclovir, foscarnet, and cidofovir.

6.12.3 Human herpesvirus 8

- Double-stranded linear with icosahedral capsid, enveloped DNA virus that belongs to a family of Herpesviridae.
- Transmitted via sexual contact, body fluids, organ transplant, and IV drug user.
- Associated with Kaposi sarcoma (KS) and non-Hodgkin lymphoma in AIDS and immunocompromised patients. Immunocompetent people in rare cases may also be infected and develop cancer.
- The virus undergoes lytic and latent cycles. In lytic cycle, it replicates in epithelial cells, blood vessels, and various organs. In latent cycle, it expresses a protein LANA-1 which inhibits tumor suppressor genes p53 and RB (retinoblastoma) and prevents apoptosis and leads to uncontrolled cell proliferation. Responsible for KS.

6.12.3.1 Kaposi's sarcoma (Fig. 6.17)

- KS is a vascular malignancy (endothelial cells). It is endemic in sub-Saharan Africa.
- Worldwide prevalence is about 5%−20%.
- More common in men who have sex with men.
- Classified into:
- Classic → Infects older male >60 years old. Indolent course usually affects skin of lower extremities, sparing lymph nodes and visceral, and is nonfatal. Lesions are

purple or red color macules that may coalesce and form violet to black plaques and nodules.

- Endemic: Affects young adults and children in Africa, more aggressive. Lymphadenopathy is present in children and is usually fatal. Adult form resembles the classic form of KS.
- Epidemic: Associated with AIDs. Very aggressive, most common form. Multiple cutaneous lesions involving face, trunk, mucosa, lymph nodes, GI tract, and lungs.
- Immunosuppressive KS: Relatively less aggressive than epidemic KS. Present with lymphadenopathy and involvement of visceral organs. Usually develops several years after the organ transplantation
- Signs and symptoms:
  - Usually, the lesions are asymptomatic but may cause bleeding if these lesions are present on the mucosa or GI tract. Shortness of breath, chest pain, cough, hemoptysis, and death if the lungs are involved.
  - Lesions are usually purple or red macules that may coalesce and form blue violet to black plaques or nodules.
- Complication:
  - Pain, bleeding, and edema.
  - Respiratory distress or death if lungs are involved.
  - Secondary malignancy.
- Diagnosis:
  - Biopsy and microscopic exam of the lesion → shows characteristic spindle-shaped cells.
  - Immunohistochemical staining to detect protein LANA-1 in spindle cells
  - PCR → detects viral DNA.

FIGURE 6.17 Kaposi sarcoma. *Source: CDC (PHIL) ID# 6436.*

- Treatment:
  - HIV infected patients→ HAART plus
  - Radiation or cryosurgery for local lesions.
  - Chemotherapy for metastasis disease.

6.13 Acquired immune deficiency

- Caused by human immune deficiency virus (HIV)
  - Targets immune cells with CD4 receptors on their surface, which include T-cells, dendritic cells, macrophages, and others
  - HIV is a single-stranded, positive-sense RNA virus, encapsulated with a bilayer lipid membrane. On the surface of the enveloped virus has glycoprotein gp 120 and 41 which binds to CD4 receptors and coreceptors CXCR4 or CCR4 on the host cell membrane.
  - Once inside the cell, the virus enzyme reverse transcriptases transcribed RNA strand to double DNA strand, which enters into the nucleus of the host cell.
  - Inside the nucleus, viral DNA attaches itself to the host DNA with the help of viral enzyme integrase.
  - This proviral DNA replicates with host DNA and transcribes viral RNA which migrates to the cell cytoplasm and is translated into viral proteins.
  - These viral proteins and viral RNA assemble into HIV virions and bud out from the cell resulting the destruction of host cells.
  - Viral enzyme protease cleaves the viral protein and converts immature virions to mature viruses, which are ready to infect other cells.
- Two subtypes: HIV-1 and HIV-2
- HIV-1 is more commonly associated with AIDS in the United States and worldwide. HIV-2 is mostly in South Africa and South Asia
- Signs and symptoms:
  - Initial infection is nonspecific and has flu-like symptoms such as fever, sore throat, myalgia, weight loss, and fatigue.
  - Chronic phase is usually asymptomatic and can last 2−10 years, during which T-cells gradually diminish.
  - AIDS is defined when one or more of the following are met.
    - When T-cells numbers <200/mcL
    - Total T-cells <14% of total lymphocyte count
    - Patients have AIDS defining illnesses
  - Relation of decreased CD4+ T cells and symptoms of AIDS (Table 6.5)
    - CD4+T numbers between 200−500/mcL. Patient experience opportunistic infections such as:
      - ➢ Lymphadenopathy
      - ➢ Oral candidiasis

  - ➢ Mononucleosis
  - ➢ Oral hairy leukoplakia
  - ➢ Activation of TB
- CD4+ T cells count <200/mcL
  - ➢ Persistent fever
  - ➢ Fatigue and weight loss
  - ➢ Diarrhea
  - ➢ ↑risk of pneumocystis jiroveci pneumonia (PCP)
  - ➢ KS
- CD4+ T cells count <100/mcL
  - ➢ Toxoplasma encephalitis, cryptococcus meningitis
- CD4+ T cells count <50/mcL
- ↑risk of cytomegalovirus (CMV) and mycobacterium avium complex (MAC)

AIDS defining illnesses

- Serious opportunistic infections
- Cancers (KS, non-Hodgkin lymphoma
- Neurological problem

- Transmission:
  - Sexual
  - IV
  - Transplacental/vertical→during birth/breast milk
- Risk of HIV transmission
  - Medical instruments infected with blood, the risk is 1 in 300 without post-exposure antiretroviral drugs. With the use of drug prophylactically ↓the risk to 1 in 1500.

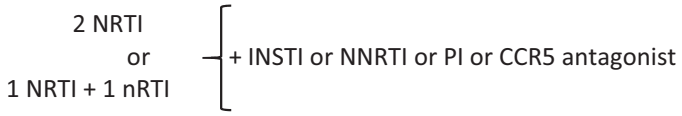
Table 6.5 Prophylactic treatment of opportunistic infection in AIDS patient.

CD4 + count	Infection	Prophylaxis	Alternate
<200	PCP	TMP/SMX	Dapsone
<100	Toxoplasmosis	TMP/SMX	Dapsone + atovaquone
	Cryptococcal	Fluconazole	
<50	CMV, MAC	Valganciclovir	
		Azithromycin	

  - Maternal transmission depends on mother's viral load. However, the average risk is 25%–35%.
  - Breast milk risk is 10%–15%
- Screening:
  - Antibody/antigen test
  - Onetime test for individuals 13–75 years old
  - Pregnant women at the time of the first visit
  - High-risk individuals should be screened every 6–12 months
- Diagnosis:
  - Antibody/antigen test
  - ELISA
  - RT-PCR
- Monitoring:
  - CD4+ T cells and viral RNA→ q 8–12 weeks for first 6 months or until HIV RNA level is undetectable level then q 3–6 month

6.14 HIV antiviral drugs

- General Guideline:



High frequency of transcription errors by HIV reverse transcriptase results in several mutations which result in drug resistance

1) Nucleoside reverse transcriptase inhibitors (NRTIs)
- Back bone of HART therapy.
- Need to be phosphorylated in vivo to be active.
- Competitively inhibit HIV reverse transcriptase.
- Cause lactic acidosis and steatohepatitis.

Abacavir (ABC) → severe hypersensitivity reaction. Do not rechallenge the patient. 100% higher risk in patients with HLA-B*57:01.
Emtricitabine (FTC) → Minimal side effects.
Lamivudine (3TC) → peripheral neuropathy and rarely pancreatitis
Zidovudine (ZDV, AZT) → Anemia and leukopenia, hepatic steatosis, pancreatitis

"ine" at the end except abacavir

2) Nucleotide reverse transcriptase inhibitors (nRTIs)
- Same as NRTI.
- Do not need to be phosphorylated in vivo to be active
  Tenofovir disoproxil fumarate (TDF) → Renal insufficiency. Do not use if Glomerular filteration rate (GFR)<60
  Tenofovir alafenamide fumarate (TAF) → less renal issue as compare to TDF
  Combination NRTI or nRTI.
  i) TAF + FTC = Descovy
  ii) TDF + FTC = Truvada
  iii) ABC + 3TC = Epzicom

"vir" at the end

3) Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- Directly bind to HIV reverse transcriptase enzyme
- Occasionally cause life-threatening rash and liver dysfunction
- Examples:
  - Doravirine → Nausea, dizziness, headache, diarrhea, abnormal dreams
  - Efavirenz (EFV)→ CNS symptoms
  - Etravirine (ETV) → Sever life-threatening rash
  - Nevirapine (NVP) → life-threatening hepatotoxicity and rash
  - Rilpivirine (RPV) → less CNS adverse effects than efavirenz

"vir" in the middle of the name

4) Protease inhibitors (PIs)
- Inhibit viral enzyme protease which is responsible for clipping of viral protein and converting immature virion to mature virus.
- Cause metabolic syndrome (↑serum glucose, hypercholesterolemia, ↑abdominal fat) nausea, vomiting, diarrhea, ↑bleeding tendency, and liver dysfunction

- Examples:
  - Atazanavir (ATZ) → rash and hyperbilirubinemia
  - Darunavir → fever, severe rash, hypersensitivity, and fever. Taken with ritonavir
  - Fosamprenavir → rash
  - Lopinavir (LPV) → altered taste, paresthesia
  - Tipranavir (TPV) → life-threatening hepatitis and intracranial hemorrhage

Names end with "navir"

5) Integrase Inhibitors (INSTIs)
- Inhibit the viral enzyme integrase which is responsible for viral DNA to fuse with host DNA.
- Mostly causes hypersensitivity reactions.
- Drugs
  - Bictegravir → Severe hypersensitivity reactions
  - Dolutegravir (DTG) → Severe hypersensitivity reaction, fetal neural tube defects
  - Elvitegravir → nausea and diarrhea
  - Raltegravir (RAL) → Severe hypersensitivity reaction

Name ends with"gravir"

6) Entry inhibitor (EI) = fusion inhibitor
- Interfere binding of HIV to CD4+ and CCR5 receptors on host cells
- Drugs:
  - Maraviroc (CCR5 inhibitor) → Myocardial infarction
  - Enfuvirtide (T-20): Bind gp 41→ hypersensitivity reaction, peripheral neuropathy, ↑risk of bacterial pneumonia, and insomnia

7) Attachment inhibitor:
- Binds to gp 120 glycoprotein on HIV envelop and inhibits viral attachment to host cell
- Drug:
- Fostemsavir → nausea and vomiting, liver dysfunction

Postexposure prophylaxis indication:

- 0.3% risk of getting infected with needle stick
- Penetrating injuries involving HIV-infected blood
- Exposure of mucus membrane
- Should start within 24–36 h

- 2 NRTI + Integrase inhibitor
  Or
  2 NRTI + Protease inhibitor
  ⟩ for 28 days

Vaccine: Not available
Pregnancy:

- TDF-FTC or TDF − 3TC + DTG or raltegravir (dolutegravir is now recommended in pregnancy). Recent studies do not show any increase risk of neural tube defect for fetus.
- NNRTI such as nevirapine or efavirenz can be added to 2 NRTI backbone.
- Didanosine, stavudine, and bictegravir should not be used in pregnancy
- Infants born of HIV-positive mother should be given 6 weeks course of zidovudine for low-risk infants.
- High-risk infants should receive multidrug treatments such as:
- Zidovudine + 3TC + Nevirapine × 6 weeks
- Zidovudine + 3TC + Raltegravir × 6 weeks

Combination products available as first-line treatment:

- Biktarvy: bictegravir-tenofovir AF-emtrictabine
- Dovato: Dolutegravir-lamivudine
- Triumeq: Abacavir-lamivudine-dolutegravir
- Descovy: Tenofovir-lamivudine + dolutegravir
- Truvada: Tenofovir DF-emtricitabine + dolutegravir
- Atripla: Tenofovir-emtricitabine-efavirenz
- Several other combinations for oral use are available
- Cabenuva: Dolutegravir-rilpivirene is available in IM form. Should start after 1 month of oral treatment then start IM once a month for 2 months then q2month thereafter.
- Indicated for adult patient with viral load suppressed <50 copies/mL and no previous treatment failure

6.15 Non—HIV antiviral drugs

Broadly classified into:

- Antiherpes drugs
- Antihepatitis drugs
- Antiinfluenza drugs
- Miscellaneous

6.15.1 Antiherpes/CMV drugs

6.15.1.1 Acyclovir

- Guanosine analog, phosphorylated by viral thymidine kinase in herpes infected cell
- Affective against herpes simplex and varicella-zoster virus, but not effective against CMV
- Uses:
  - Primary and recurrent oral, genital, and ocular herpes infection
  - Drug of choice for herpes
  - Varicella infection including, pneumonia.
  - Zoster (shingles) infection, including ophthalmicus
- Adverse effects:
  - Nephrotoxicity → in high doses. Precipitate in renal tubules
  - Neurotoxicity → confusion, hallucination, lethargy, seizure
  - Excretion is renal base, ↓the dose in kidney's dysfunction
  - Other side effects are nausea, vomiting, diarrhea, rash, and muscles cramp.

6.15.1.2 Famciclovir/valacyclovir

- Same as acyclovir, but better oral absorption
- Famciclovir metabolized to penciclovir

6.15.1.3 Ganciclovir

- Guanosine analog, phosphorylated by human thymidine kinase
- Active against CMV, also active against herpes viruses.
- More toxic than acyclovir.
- Neutropenia and thrombocytopenia are major concerns.
- Black box warnings → cytopenia, carcinogenic

6.15.1.4 Valganciclovir

- Prodrug converted to ganciclovir in vivo. Same profile as ganciclovir

6.15.1.5 Cidofovir

- Cytosine analog, phosphorylated into active form by host cell kinases
- Active against CMV, HSV, EBV, adenovirus, HPV, and JC virus

- However, FDA-approved use is for CMV retinitis in HIV patients
- Drug of choice for smallpox
- Major side effects are nephrotoxicity and neutropenia

6.15.1.6 Foscarnet

- Pyrophosphate analog inhibits DNA polymerase and reverse transcriptase.
- Used for the treatment of CMV infection
- Also, used against acyclovir-resistant HSV strain
- Major side effects are nephrotoxicity, anemia, elevated liver enzymes, electrolyte abnormality, penile, and oral ulcers
- Dose adjustment is required in kidney disease

6.15.1.7 Fomivirsen

- Inhibits CMV and used for CMV retinitis. Not the first choice
- Injected into eyes
- Ocular inflammation and increased eye pressure are common side effects.

6.15.2 Anti-hepatitis C virus drugs

- NS3/4A -Protease inhibitor (PI) ——previr (p for PI)
  Prevent cleavage of necessary proteins for replications
  - Glecaprevir
  - Grazoprevir
  - Paritaprevir
  - Simeprevir
  - Voxilaprevir
- NS5A inhibitor. Inhibits NS5A protein which is necessary for viral replication —asvir (a for A)
  - Elbasvir
  - Pibrentasvir
  - Ombitasvir
  - Velpatasvir
  - Daclatasvir
- NS5B polymerase inhibitors —buvir (b for NS5B)
  - Sofosbuvir
  - Dasabuvir

HCV regimens include 2–3 direct acting antiviral drugs with different classes or mechanism of action.

None of the above-mentioned antivirals are used alone and are not available.

- Combination available products are as follows:
  - Sofosbuvir/ledipasvir (Harvoni) → genotypes 1, 4, 5, and 6

- Elbasvir/grazoprevir (Zepatier) → genotypes 1 and 4
- Glecaprevir/pibrentasvir (Mavyret) → genotypes 1–6
- Most common side effects are headache, nausea, fatigue, abdominal pain, and diarrhea.

6.15.2.1 Summary of hepatitis C drugs (Table 6.6)

Table 6.6 Hepatitis C drugs.

Regimen	Genotype	Remarks
Glecaprevir-pibrentasvir 300–120 mg daily × 8 weeks	Any type	Treatment naïve, with/without cirrhosis
Sofosbuvir-velpatasvir 400–100 mg daily × 12 weeks	Any type	Treatment naïve, with/without cirrhosis
Elbasvir-grazoprevir 50–100 mg daily × 12 weeks	1a, 1b, 4	Treatment naïve, with/without cirrhosis
Sofosbuvir-ledipasvir 400–90 mg daily × 8–12 weeks	1a, 1b, 4, 5, 6	Treatment naïve, with/without cirrhosis
Sofosbuvir-velpatasvir-voxilaprevir 400 mg–100 mg–100 mg daily × 12 weeks	Any type	Sofosbuvir-based or elbasvir/grazoprevir treatment failure with or without cirrhosis
Glecaprevir-pibrentasvir 300–120 mg daily × 16 weeks	Any type	Same as above
Glecaprevir-pibrentasvir 300–120 mg daily + sofosbuvir 400 mg daily + ribavirin 1000–1200 mg per day for 16–24 weeks	Any type	Multidrug failure, with or without cirrhosis
Sofosbuvir-velpatasvir-voxilaprevir 400 mg–100 mg–100 mg daily × 24 weeks + ribavirin 1000–1200 mg per day divided into 2 doses × 24 weeks	Any types	Multidrug failure, with or without cirrhosis

6.15.3 Antiinfluenza drugs

6.15.3.1 Amantadine/rimantadine

- Interferes with viral replication and disrupts transmembrane viral M2 protein, which prevents viral entry into the host cell.
- Used for the treatment of influenza virus type A. However, high level of resistance minimized the use.
- Not effective against influenza virus B
- CNS side effects such as nervousness, anxiety, and lightheadedness are common.
- Rimantadine has fewer CNS effects
- Anticholinergic effects: dry mouth and urinary retention in older people

6.15.3.2 Oseltamivir/Zanamivir/Peramivir

- Neuraminidase inhibitors
- Use for influenza virus types A and B
- Oseltamivir is oral, zanamivir is nasal, and peramivir is IV formulation

6.15.4 Miscellaneous antiviral agents

6.15.4.1 Ribavirin

- Guanosine analog, phosphorylated into active form by kinases in human cells
- Effective against RSV virus and hepatitis C virus with interferon
- Cause hemolytic anemia

6.15.4.2 Interferon alpha-a2b

- Use in the treatment of hepatitis C and hepatitis B
- Use in hepatitis C is outdated as direct acting antiviral drugs are more effective with fewer side effects
- Flu-like symptoms at the start of therapy are common. Other serious side effects, such as neuropsychiatric, autoimmune reaction, or ischemia, require discontinuation of the therapy.

6.15.4.3 Trifluridine

- Nucleoside thymidine analog
- Eye drop use for HSV corneal infection

6.16 Summary of viral infection

Virus	Infection	Family	RNA/DNA	Strand	Comments
Viruses affect CNS					
Poliovirus (fecal—oral route)	Polio	PICORNA viridae	RNA	+	Worldwide. Vaccine available
WEE (mosquito-borne)	Encephalitis	TOGA viridae	RNA	+	North and South America.
EEE (mosquito-borne)	Encephalitis	TOGA viridae	RNA	+	North and South America
VEE (mosquito-borne)	Encephalitis	TOGA viridae	RNA	+	South America
St. Louis encephalitis (mosquito-borne)	Encephalitis	FLAVI viridae	RNA	+	North and South America
Japanese encephalitis	Encephalitis	FLAVI viridae	RNA	+	Southeast Asia, Japan, Korea, China, Philippines
West Nile Virus (mosquito-borne)	Encephalitis	FLAVI viridae	RNA	+	Africa, Middle East, India, Russia, US, Canada. Vaccine available
California encephalitis Virus (mosquito borne)	Encephalitis	BUNYA viridae	RNA	−	Worldwide. No vaccine, no therapy available

—cont'd

Virus	Infection	Family	RNA/ DNA	Strand	Comments
Flavivirus. Tick-borne encephalitis (tick ixodes)	Encephalitis	FLAVI viridae			Eastern and Central Europe. Vaccine is available
Rabies virus	Rabies	RHABDO viridae	RNA	−	Worldwide. Vaccine and immune globulin available
JC virus	PML	PAPOVA viridae	DNA	N/A	Worldwide
Respiratory viruses					
Influenza virus A, B, C	Influenza	ORTHOMYXO viridae	RNA	−	Worldwide, seasonal usually in winter. Vaccine available
Parainfluenza virus	Acute bronchitis, pneumonia,croup	PARAMYXO viridae	RNA	−	Worldwide, outbreak usually in autumn
Adenovirus	Pneumonia, conjunctivitis, gastroenteritis, hemorrhagic cystitis	ADENO viridae	DNA	Double stranded	Worldwide
Respiratory syncytial virus	Bronchiolitis, pneumonia	PARAMYXO viridae	RNA	−	Worldwide, no vaccine available
Rhinovirus	Common cold	PICORNA viridae	RNA	+	Worldwide, no vaccine
Coronavirus	Upper respiratory tract infection, MERS, SARS, COVID-19	CORONA viridae	RNA	−	Worldwide, pandemic. Vaccine available for COVID-19
Mumps virus	Mumps, orchitis, meningitis, pancreatitis	PARAMYXO viridae	RNA	−	Worldwide, vaccine MMR
Viruses associated with gastroenteritis					
Rotavirus	Watery diarrhea ± vomiting	REO viridae	RNA	Double stranded	Worldwide, infects young children usually in daycare
Norovirus or Norwalk virus	Same as above	CALI viridae	RNA	+	Worldwide, children and adults, especially cruise ships
Astrovirus	Same as above	ASTRO viridae	RNA	+	Worldwide
Exanthematous viruses					
Rubeola virus	Measles, pneumonia, enecephalitis,	PARAMYXO viridae	RNA	−	Worldwide, vaccine MMR
Rubella virus	German measles, TORCH	TOGA viridae	RNA	+	Worldwide, vaccine MMR
Human parvovirus B19	Erythema infectiosum, aplastic crises	PARVO virus	DNA	Single stranded	Worldwide, no vaccine
Human herpes virus types 6 and 7	Roseola infantum, encephalopathy, otitis media	HERPES viridae	DNA	Double stranded	Usually infect children, no vaccine
Viruses cause hepatitis					
Hepatitis A virus	Acute hepatitis	PICORNA viridae	RNA	+	Worldwide, fecal—oral route, vaccine available
Hepatitis B	Acute, chronic, and fulminating hepatitis	HEPADNA viridae	DNA	Double stranded	Blood transfusion, organ transplants, IV drug user, risky sexual behavior, infant born of infected mother, vaccine available

Continued

—cont'd

Virus	Infection	Family	RNA/ DNA	Strand	Comments
Hepatitis C	Chronic hepatitis	FLAVI viridae	RNA	+	Same as above
Hepatitis D	Acute and fulminating hepatitis	None	RNA		Defective virus, cannot replicate itself. No vaccine but HBV provides protection
Hepatitis E	Acute and fulminating hepatitis	HEPE viridae	RNA	+	Fecal—oral route, causes fulminating hepatitis in pregnant women, vaccine available in China
Viruses cause hemorrhagic fever					
Yellow fever virus Mosquito borne	Yellow fever	FLAVI viridae	RNA	+	Endemic in South America and Sub-Saharan Africa. Vaccine available for high-risk patients
Dengue fever virus (mosquito borne)	Dengue fever	FLAVI viridae	RNA	+	Southeast Asia, Caribbean island, Porta-Rico, US, Virgin island. Vaccine available
Ebola and Marburg virus	Acute hemorrhagic fever	FILO viridae	RNA	+	Central and West Africa. Vaccine available for high risk areas.
Hantavirus	Hemorrhagic fever with renal syndrome, hantavirus pulmonary syndrome	BUNYA viridae	RNA	−	Worldwide, rodents are the carriers and shed virus in the urine and feces. Ribavirin
Viruses cause mucus membrane infection					
Herpes simplex virus types 1 and 2 (HSV)	Cold sore, genital herpes, herpetic whitlow, keratoconjunctivitis	HERPES viridae	DNA	Double stranded	Worldwide, sexually transmitted disease. No vaccine available. Acyclovir, famciclovir, Valacyclovir
Varicella-zoster virus (human herpes virus type 3)	Chicken pox, shingle	HERPES viridae	DNA	Double stranded	Acyclovir, Valacyclovir, Famciclovir. Vaccine for shingles
Human papilloma virus	Warts, genital warts, cervical cancer, and cancer in other areas	PAPOVA viridae	DNA	Double stranded	Sexually transmitted disease, vaccine available, various treatment options
Viruses infect multiple system					
Epstein—Barr virus (HHV-4)	Mononucleosis, Burkitt lymphoma, nasopharyngeal carcinoma	HERPES viridae	DNA	Double stranded	No vaccine available
Cytomegalovirus (CMV)	mononucleosis, congenital infection, retinitis, pneumonia, hepatitis, colitis	HERPES viridae	DNA	Double stranded	Ganciclovir, valganciclovir, foscarnet. No vaccine
Coxsackievirus	Hand-foot and mouth disease, herpangina, aseptic meningitis, pericarditis, neonatal sepsis	PICORNA viridae	RNA	+	No vaccine
Human immunodeficiency virus (HIV)	Autoimmune deficiency syndrome (AIDS)	RETRO viridae	RNA	+	No vaccine, various antiviral treatments available

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7 Fungus

7.1 Fungal cell

- Eukaryotic cell contains membrane-bound organelle (Fig. 7.1).
- No chlorophyll and cannot generate energy through photosynthesis like plant cells.
- Rigid cell wall surrounded the cell membrane composed of glucans and chitin.
- Heterotroph cannot produce their own food.
- Phospholipid bilayer membrane contains ergosterol.
- Cell wall mostly forms beta-1,3-glucans links, but other links are also present depending on fungal species.

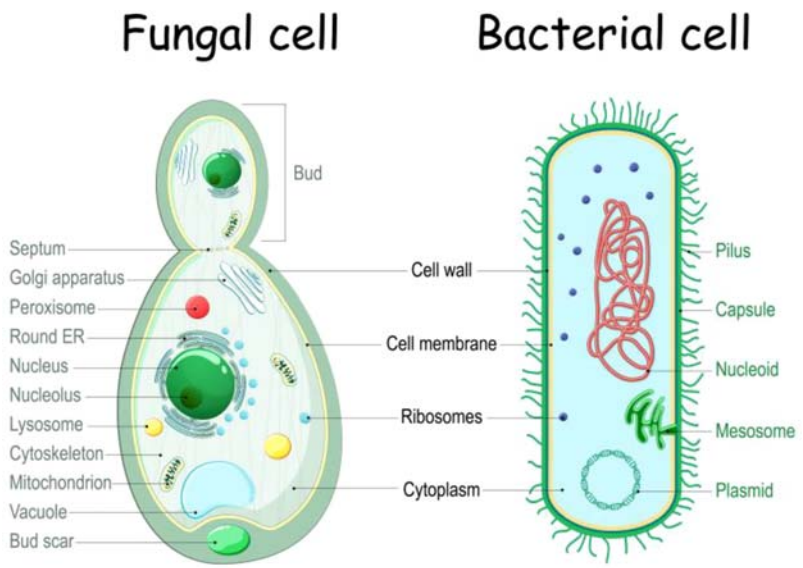

FIGURE 7.1 Fungal and bacterial cell.

Infectious Diseases. https://doi.org/10.1016/B978-0-443-18742-1.00405-X
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7.2 Classification

Yeast	Mold	Dimorphic fungus	Dermophytes
Unicellular	Multicellular	Exists as both yeast and mold	Metabolized and substrate on keratin
Occasionally organized into hyphae and pseudohyphae	Organized into hyphae	Exists as a mold in the environment and as a yeast in the host	Named accordingly to the site of infection
Usually white in color	Multicolor	Region-specific[a]	
Reproduce asexually by budding out	Reproduce sexually and asexually. Produce spores.	Histoplasma	Head—tina capitis
a) Candida	**a)** Aspergillus	Blastomyces	Trunk—tina corporis
C. albicans (most common).	**b)** Mucorales	Coccidioides	Groin—tine cruris
C. glabrata	• Mucus	Paracoccidioides	Foot—tina pedia
C. krusei	• Rhizopus	Sporothrix	Folded skin—candida intertrigo
C. parapsilosis	• Rhizomucor		Nail—onychomycosis
C. tropicalis			Tina versicolor
b) Cryptococcus			
C. neoformans (most common)			
C. gattii			

[a]Histoplasma and blastomyces infections are common in the southeast around the Mississippi river. Coccidioides infections are common in the southwest part of the USA.

7.3 Yeast

- Yeast are fungi that reproduce by budding and can convert sugar into alcohol and carbon dioxide.
- Comprises Candida and Cryptococcus

7.3.1 Candida

- Includes several species.
- *Candida albicans* is the most common.
- Part of normal flora in the oropharynx, gastrointestinal (GI) tract, and vagina.
- Causes opportunistic infection in immune-compromised patients or when normal flora is disrupted.
- Candida infection can be classified into:
  1. Noninvasive infections
  2. Invasive infections

7.3.1.1 Noninvasive infections

- Oropharyngeal candidiasis (thrush) (Fig. 7.2).
  - White soft plaque in the mouth or pharynx that can be rubbed off
  - Pain during swallowing if the oropharynx involved
  - Risk factors: Use of antibiotics, xerostomia, immunosuppression, and use of corticosteroids.
  - Diagnosis:
    - Clinical
    - Microscopic examination with KOH shows characteristic fungal structures
  - Treatment:
    - Nystatin suspension
    - Fluconazole
    - Second choice → echinocandin for severe cases
- Esophagitis:
  - Symptoms are similar to thrush in the mouth.
  - Mostly infects immunodeficiency patients.
  - Pain in swallowing is the most common symptoms patients complain about.
  - Treatment is the same as for thrush.
- Vaginitis:
  - Thick, white, cottage-cheese like discharge
  - Pruritis but painless
  - Risk factors: Use of antibiotics, local use of douches, creams, or powder that change the normal flora. Immunosuppression and use of corticosteroids

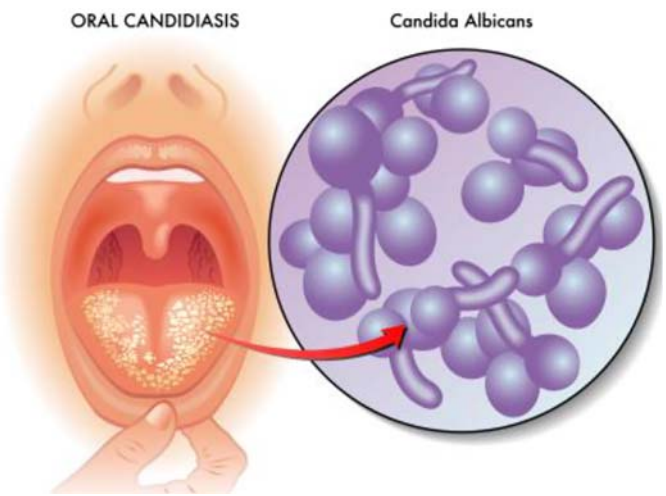

FIGURE 7.2 Oral candidiasis.

  - Treatment:
    - Local azole cream, for example, miconazole, itraconazole cream, etc.
    - Oral fluconazole
- Chronic mucocutaneous candidiasis:
  - Chronic conditions result from repeated fungal infections such as recurrent oral thrush, onychomycosis, vaginitis, and chronic skin lesions

7.3.1.2 Invasive candidiasis

- Candidemia → presence of candida in blood. Symptoms vary from fever to septic shock and are indistinguishable from bacterial infection. However, clues for fungus infection include but are not limited to observing any skin, eye, or muscle fungus infection, which could be disseminated via blood especially in neutropenic patient.
- Endocarditis → mostly in intravenous (IV) drug abuser, infect the tricuspid valve.
- Meningitis: Symptoms are the same as acute bacterial meningitis
- Esophageal candidiasis → AIDS patients
- Candida endophthalmitis → eye infection that may result in permanent scarring and blindness.
- Urinary tract infection
- Osteoarticular infections
- Pneumonia
- Risk factors:
  - Neutropenia
  - Diabetes mellitus
  - Graft versus host disease
  - Major surgery
  - Use of catheters
  - Use of broad-spectrum antibiotics, corticosteroids, and cytotoxic chemotherapy
  - Indwelling IV lines
  - Mechanical ventilation
  - Long-term hospitalization in ICU
  - Use of TPN
- Diagnosis:
  - Histopathology
  - Culture
  - Beta-glucan testing
  - T2 Candida Panel → magnetic resonance assay that detects *C. albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, *Candida glabrata*
- Treatment:
  - If the patient is stable, infection is not severe and caused by *C. albicans* than use fluconazole.
  - If the patient is critically ill or infected with a species other than *C. albicans* or *C. parapsilosis*, then use echinocandin.
  - Alternate: Amphotericin.

7.3.2 Cryptococcus

- Encapsulated yeast.
- Present all over the world.
- Found in soil contaminated with birds dropping like pigeons, chickens, and rotten vegetables.
- Facultative intracellular fungi exist in asexual form (yeast) and sexual form (teleomorphs).
- Transmission is usually inhaling spores from the environment or reactivation of the previous infection when a patient becomes immunocompromised.
- Cause meningitis and pneumonia in immune-compromised patients.
- Two species of Cryptococcus commonly cause infection in humans. Cryptococcus neoformans is the most common.
- *Cryptococcus gatti* is less common and found in tropical and subtropical regions. It is associated with infections in immunocompetent patients.

7.3.2.1 Cryptococcal meningitis

- May cause no meningeal sign.
- Incubation period is usually 1–2 weeks and includes fever, malaise, headache, stiff neck, photophobia, nausea, and vomiting.
- Headache slowly progressed to altered mental status, blurred vision, confusion, agitation, and behavioral changes.
- Signs and symptoms may also result from cerebral edema.
- Diagnosis:
  - Lumbar puncture (LP) → increase protein, increase leukocytes with monocytes predominant, and decrease cerebrospinal fluid (CSF) glucose
  - Cryptococcal antigen is positive in blood or CSF
  - Microscopic exam
  - India ink stain: capsule visualized with halo
  - Culture
- Treatment: Amphotericin B ± flucytosine x two weeks followed by fluconazole until symptoms resolved.

7.3.2.2 Cryptococcal pneumonia

- May be asymptomatic.
- Usually have cough and nonspecific symptoms.
- In patients with AIDS, symptoms are severe and may be life-threatening.
- Diagnosis:
  - Chest X-ray → lobular pneumonia
- Culture
- Cryptococcal antigen testing

- Treatment:
  - Fluconazole
  - AIDS patient, treat with amphotericin B followed by fluconazole

www.images.google.com see chest X-ray for cryptococcal pneumonia (lobular pneumonia)

7.4 Molds

- Microscopic, multinucleated, long filamentous branching structure composed of hyphae and spores (Figs. 7.3 and 7.4).
- Diverse groups and mostly nonpathogenic.
- Two major groups cause disease in humans.
  1. Aspergillus
  2. Mucorales
     - *M. rhizopus*
     - *M. rhizomucor*
     - Mucor
- Both groups cause rhinosinusitis and pulmonary infection in immune-compromised patients

7.4.1 Aspergillus

- Aspergillus is a mold found in soil, water, and other decaying organic matter. Exposure to the fungus spores may result in various illnesses called Aspergillosis. In immunocompetent patients, it doesn't cause any symptoms except allergic aspergillosis. However, in immunocompromised patients, it may cause invasive aspergillosis (lung infection) or chronic pulmonary aspergillosis.

FIGURE 7.3 Mold.

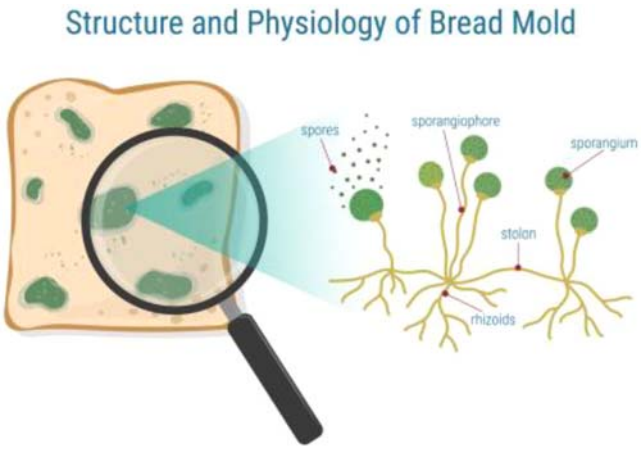

FIGURE 7.4 Mold.

- Risk factors:
  - Immunodeficiency
  - Stem cell transplants
  - Malignancy
  - Organ transplant
  - Use of immunosuppressive agents
  - Asthma
  - Cystic fibrosis
  - Chronic lung disease
  - Tuberculosis or sarcoidosis

7.4.1.1 Pulmonary aspergillosis

- Can be classified into:
  - Acute invasive pulmonary aspergillosis: Manifests with cough, fever, hemoptysis, and pleuritic chest pain. If untreated rapidly progresses to respiratory failure.
  - Chronic pulmonary aspergillosis: Indolent coarse, mild fever, cough, chest pain, hemoptysis, weight loss, and fatigue.
- Other symptoms:
  - Extrapulmonary aspergillosis: Involves the liver, kidney, and brain. Usually rapidly fatal.
  - Sinus aspergillosis: Involves nose, sinuses, gingiva, and palatal plate. Causes necrosing lesions.
  - Aspergilloma: Fungus ball in the lung
- Diagnosis:
  - Histopathology
  - Culture

  - Galactomannan antigen test on serum or bronchoalveolar lavage
  - Polymerase chain reaction (PCR)
- Treatment: Amphotericin, voriconazole ± echinocandin for invasive aspergillosis treatment.

7.4.2 Mucormycetes

- Includes genera Rhizopus, Rhizomucor, and Mucor.
- Responsible for mucormycosis, which is a rare but serious fungal infection.
- Usually, it causes sinusitis and lung infection.
- Invades the blood vessels and causes thrombosis, which result in rapid tissue necrosis.
- Species included are Mucor species, Rhizopus species, and *Cunninghamella bertholletiae*.
- Mucormycetes are commonly found in soil and decaying leaves, vegetables, and fruits.
- Transmission is usually inhalation or ingestion of spores from the environment.
- Risk factors:
  - Immunocompromised
  - Uncontrolled diabetics
  - Malignancy
  - Stem cell transplant
  - Solid organ transplants
  - Neutropenia
  - Skin trauma or burns
  - IV drug user
  - Malnourishment and premature infants

7.4.2.1 Mucormycosis

- Form of mucormycosis:
  - Rhinocerebral mucormycosis: Most common form.
    - Unilateral facial swelling.
    - Headaches, nasal congestion or pain, nasal discharge, and fever.
    - Later, as the infection spreads, ptosis, proptosis, loss of extraocular muscles movement, and vision disturbance are common sign.
    - Necrotic black lesions on the hard plate or nasal turbinate or black pus from the eyes are diagnostic.

- Pulmonary mucormycosis:
  - Nonspecific symptoms
  - Fever, cough, chest pain, and dyspnea
  - Cavitation and hemoptysis due to angioinvasion and tissue necrosis
- Cutaneous mucormycosis:
  - People with burns or skin trauma are infected with the fungus.
  - The fungus stimulates acute inflammatory response, which results in pus, abscess, tissue swelling, and necrosis.
  - Initially, the lesion appears red and indurated and later progresses to black eschar.
- Gastrointestinal mucormycosis:
  - Less common than other forms.
  - Ingestion of mold, especially in malnutritional and premature infants.
  - Symptoms are similar to necrotizing enterocolitis, such as abdominal pain, distension, nausea, vomiting, and bleeding. Diagnosis could be challenging.
- Disseminated mucormycosis:
  - Other forms of mucormycosis especially pulmonary infection in neutropenic patient may spread to other organs such as brain, spleen, heart, skin, etc.
- Diagnosis:
  - Examination of tissue sample → broad, ribbon-like nonseptate hyphae
  - Culture
  - PCR
- Treatment:
  - Amphotericin B
  - Surgical debridement

7.5 Dimorphic fungus

- Acts as either yeast or molds.
- Present in the environment as a mold, but, when inhaled, grows as a yeast in the host and mostly causes pulmonary infections in immune-compromised patients.
- Region-specific.

7.5.1 Histoplasma capsulatum

- Found worldwide, common in the Midwest and south of the United States, Ohio, and Mississippi river valley.
- Present in birds or bats dropping.
- Transmitted via inhalation of conidia or mycelial form.
- Inside the host, changes to yeast and is taken by macrophages, where it survives and reaches to the lungs, and causes bronchopneumonia.

- Incubation period is usually 3–17 days. However, most of the people who expose to fungus didn't get sick.
- Three forms:
  - Acute primary histoplasmosis:
    - Fever, cough, malaise, chest pain, and all other signs of acute pneumonia.
  - Chronic cavitary histoplasmosis:
    - Manifested by pulmonary lesion and caseous necrosis, usually apical, and resembles tuberculosis. Symptoms of cough and dyspnea worsen.
  - Progressive disseminated histoplasmosis:
    - Spread all over the body, including the reticuloendothelial system, leading to hepatomegaly and lymphadenopathy. As the disease progress, it involves bone morrow, central nervous system (CNS), and GI system. Also, responsible for endocarditis, meningitis, and ocular histoplasmosis.
- Risk factors:
  - Immunocompromised
  - CD4+ cell count <150 cells/mm^3 in HIV patients
  - Traveling to endemic areas
  - Comorbidity
  - Extreme age
  - Living in high-prevalence area such Midwest, Ohio, or Mississippi river valley
  - Exploring caves
  - Cleaning or playing the area with birds or bat dropping
- Diagnosis:
  - Histopathology and culture
  - Antigen testing in the urine or serum
  - Antibody test
  - CXR: Shows diffuse nodular densities in acute infection, cavitary lesions in chronic, and hilar adenopathy with diffuse nodules in progressive disseminated disease
  - PCR
- Treatment:
  - Itraconazole for mild to moderate disease in immune competent patient.
  - Amphotericin B $\times$ 14 days then followed by itraconazole $\times$ 1 year for severe disease or in immune compromised patient.

7.5.2 Blastomyces dermatitidis

- Found in the Midwest and south of the United States, particularly in the area of Ohio and Mississippi rivers and Canada.
- Causes pulmonary and extrapulmonary infections called blastomycosis. Inoculate soil and decaying organic matter such as wood and leaves. People get infected by inhaling the spores. Most of the infected persons remain asymptomatic.

- Pulmonary infection:
  - productive or dry cough, chest pain, dyspnea, fever, chills, sweating, and can progress to acute respiratory distress syndrome (ARDS).
- Extrapulmonary symptoms
  - include skin lesions, bone lesions, and genital lesions. Disease may spread to CNS and cause brain abscess or meningitis.
- Risk factors:
  - Immunocompromised
  - Living in the endemic area
  - Exposure to contaminated soil
- Diagnosis:
  - Culture
  - Blastomyces urine antigen
  - Chest X-ray
  - PCR
- Treatment:
  - Itraconazole for mild to moderate disease in immune-competent patients.
  - Amphotericin B $\times$ 14 days then, followed by itraconazole $\times$ 1 year for severe disease or in immune-compromised patients.

7.5.3 Coccidioides immitis/posadasii

- Found in the southwest US and Mexico.
- People get infected by inhaling the spores from contaminated soil.
- Mostly infects immune-compromised patients.
- It causes both pulmonary and extrapulmonary infections called coccidioidomycosis.
- Incubation period is usually 1–3 weeks after the exposure.
- Acute pulmonary symptoms.
  - Fatigue, dyspnea, headache, cough, night sweating, and myalgia are common.
- Extrapulmonary symptoms.
  - Bone and joint infection, soft tissue, and meningitis
- Diagnosis:
  - Cultures
  - Microscopic exam
  - Serologic testing
  - Chest X-ray
- Treatment:
  - Amphotericin till clinical improvement and then use itraconazole or fluconazole.
  - For chronic pulmonary disease, triazole $>$1 year.
  - Meningitis: Lifelong therapy with a fluconazole. Alternate is amphotericin.

7.5.4 Sporothrix

- Present throughout the world.
- Infection is through minor cuts and abrasions in the skin rather by inhalation.
- Several species, including *Sporothrix brasiliensis*, *Sporothrix globose*, and *Sporothrix mexican* are associated with Sporotrichosis; therefore, it is named *Sporothrix schenckii* complex.
- Found in soil, plants, marine animals, woods, decaying vegetation, and organic matter.
- Also infects animals such as cats, dogs, swine, horses, rats, and armadillos.
- Organisms inoculate into the skin and can affect anyone especially seen to effects florists, gardeners, and nursery workers.
- *S. schenckii* is a dimorphic fungus that exists in a hyphal form at a temperature less than 37° and as yeast at a temperature above 37°.
- Organism has some virulent factors such as thermotolerance, ergosterol peroxide, and melanin. The ergosterol peroxide plays an important role in evading the species from reactive oxygen during phagocytosis.
- Risk factors:
  - Handling of plants, decaying vegetation, and contaminated soils
  - People with COPD
  - Alcoholics
  - History of steroid use
  - Diabetic and immunocompromised

7.5.4.1 Sporotrichosis (Fig. 7.5)

- Incubation period is several days to 3 months after exposure
- Infections have several forms, including cutaneous, pulmonary, and disseminated.
- Lymphocutaneous is the most common form. A primary lesion is usually a painless, small papule, which grows and becomes necrotic and ulcerates. Few weeks later, infection reaches to the nearby lymph nodes, which become enlarged. Without treatment, overlying skin reddens, necrose form abscess, ulcerates, and result in bacterial superinfection.
- Pulmonary sporotrichosis: Symptoms include cough, low grade fever, and weight loss. Usually infect immunocompromised patients or patients with lung issues.
- Disseminated sporotrichosis: Infection spread to liver, spleen, bone, lungs, meninges, and blood.
- Diagnosis:
  - Skin biopsy
  - Culture
- Treatment:
  - Itraconazole for mild to moderate infection. Amphotericin for severe infection.

FIGURE 7.5 Cutaneous lesion caused by *Sporothrix schenckii*. *Source: CDC (PHIL).*

7.6 Dermatophytes

- Metabolized and subcrust on keratin
- Usually cause skin infection
- Named according to the area infected
  - Head → tinea capitis (Fig. 7.6).
  - Trunk → tinea corporis (ringworm) (Fig. 7.7).
  - Genital tinea cruris (jock itch)
  - Fold skin → candida intertrigo
  - Nail → onychomycosis
  - Tina versicolor → pigmented and nonpigmented
- Drug: Topical or oral azole

FIGURE 7.6 Tinea capitis. CDC.

FIGURE 7.7 Ring worm.

- ***Risk factors for fungal infection:***

Major	Minor
Bone marrow transplant	Any chemotherapy
Chemotherapy for hematological malignancies	Critical illness
Solid-organ transplants	Mechanical ventilation
AIDS	Mechanical ventilation
	Venous catheters
	Hemodialysis
	TPN
	Diabetes
	Recent broad-spectrum antibiotics
	Malnutrition

- Diagnosis:
- Clinical
- Microscopic
- Add KOH on skin scrapes, which dissolve keratin and cellular component. Observe under microscope → characteristic hyphae, septa, spores, etc.
- Calcofluor white fluorescent stain which binds to chitin
- India ink for cryptococcal meningitis
  Culture → 50% sensitivity. Takes up to a week to a month to get the result
- Antigen antibody test
- Galactomannan test for aspergillus

7.7 Summary

Pathogen	Disease	Antifungal	
	Yeast	**First choice**	**Second choice**
Candida albicans	Oropharyngeal candidiasis, esophagitis, vaginitis, chronic mucocutaneous candidiasis, candidemia, endocarditis, meningitis, esophageal candidiasis, candida endophthalmitis, urinary tract infection, pneumonia, and bone infection	Fluconazole for mild to moderate infection caused by C. albicans For sever infection or caused by other than C. albicans species use Echinocandin	Amphotericin B
Cryptococcus	Meningitis and pneumonia	For meningitis: Amphotericin B ± flucytosine × 2 weeks followed by fluconazole	None
		For pneumonia: fluconazole or echinocandin	Amphotericin B for pneumonia
Pathogen	**Disease**	**Antifungal**	
	Mold	**First choice**	**Second choice**
Aspergillus	Pulmonary aspergillosis	Voriconazole ± echinocandin	Amphotericin B
Mucorales	Mucormycosis	Amphotericin B	None
Dimorphic fungus			
Histoplasma capsulatum	Histoplasmosis	Itraconazole for mild to moderate infection. Amphotericin B × 14 days then itraconazole × 1 year for severe infection	None
Blastomyces dermatitidis	Blastomycosis	Itraconazole for mild to moderate infection. Amphotericin B × 14 days then itraconazole × 1 year	None
Coccidioides	Pneumonia. joint and bone infection, and meningitis	Amphotericin followed by itraconazole or fluconazole	Chronic pulmonary disease → triazole >1 year Meningitis → lifelong therapy with fluconazole.
Sporothrix	Rose gardener disease	Itraconazole for mild to moderate infection	Amphotericin B for severe infection
Dermatophytes			
Tina capitis	Infection of head	Topical cream or lotion such as clotrimazole, Lamisil, and nystatin	Oral azole
Tina corporis	Infection of trunk	Topical cream or lotion such as clotrimazole, Lamisil, and nystatin	Oral azole
Tina cruris	Infection of genitals	Topical cream or lotion such as clotrimazole, Lamisil, and nystatin	Oral azole
Candida intertrigo	Infection of skin folds	Topical cream or lotion such as clotrimazole, Lamisil, and nystatin	Oral azole
Tina versicolor	Multicolor skin	Topical cream or lotion such as clotrimazole, Lamisil, and nystatin	Oral azole
Onchomycetes	Infection of nail	Topical cream or lotion such as clotrimazole, Lamisil, and nystatin	Oral azole

7.8 Antifungal drugs

Three major class.

7.8.1 Polyenes

Bind to ergosterol and cause pores in the cell membrane.

7.8.1.1 Amphotericin

- Broad spectrum
- Activity against
  - Candida species
  - Cryptococcus
  - Aspergillus species
  - Mucorales species
  - Dimorphic fungi
  - Resistance is very uncommon
- Toxicity:
  - Nephrotoxic → reversible
  - Infusion reaction → fever/chill/rigors, nausea, and vomiting
  - Electrolytes abnormalities → decrease K and Mg, normal gap metabolic acidosis.
  - Phlebitis
  - Anemia
  - Preparation: Lipid base amphotericin is less toxic → decreases nephrotoxicity.

7.8.2 Azoles

Inhibit lanosterol 14 alpha-demethylase, which inhibits ergosterol synthesis in the fungal cell.

For example: Fluconazole, itraconazole, and voriconazole.

7.8.2.1 Fluconazole

- First choice for *C. albicans* infection
- Consolidation therapy for meningitis after amphotericin + flucytosine
- Mild to moderate infection caused by coccidioidomycosis
- Second line therapy for blastomycosis and histoplasmosis non-CNS disease

7.8.2.2 Itraconazole

- Used against dimorphic fungi for mild to moderate infections

7.8.2.3 Voriconazole

- Aspergillus infection with or without echinocandin
- Toxicity:
  - Hepatotoxicity → elevated LFT
  - Drug interactions
  - Alopecia → fluconazole
  - Hypertension, hypokalemia, edema →itraconazole
  - Neurotoxicity, visual changes, photosensitivity → voriconazole

7.8.3 Echinocandins

Inhibit beta 1,3 glucan synthesis and inhibit cell wall
For example: Caspofungin and micafungin

- Effective against Candida species but not cryptococcus
- Aspergillus infection with the combination of voriconazole.

Toxicity: Not very common.

7.9 Quick reference of antifungal drugs

	Yeast		Mold		Dimorphic fungus	
Drug	**Candida**	**Cryptococcus**	**Aspergillus**	**Mucorales**	**Blastomyces/ histoplasma**	**Coccidioides**
Amphotericin	++	++	++	++	++	++
Azole						
Fluconazole	++	++	−	−	+	++
Itraconazole	−	−	+	−	++	++
Voriconazole	+	−	++ Use with echinocandins	−	−	−
Echinocandins	++	++	Use with voriconazole	−	−	−

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8 Parasitic infections

Parasites are the living organism that lives inside the living host and receives nutrition from them.

8.1 Classification

- Protozoa
- Microsporidia
- Worms (helminths)
  - Nematodes (roundworms)
  - Platyhelminthes (flatworm)
    - ➢ Cestodes
    - ➢ Trematodes
- Ectoparasites → scabies and lice (discussed in skin Section 9.13.9)

8.2 Protozoa

Single cell organism responsible for various diseases in humans. Classified into:

(1) Intestinal
(2) Extraintestinal

8.2.1 Intestinal protozoa (Fig. 8.1)

- Usually responsible for gastroenteritis with or without blood.
- Transmission is via fecal oral route. Common in unhygienic areas and underdeveloped countries.
- Outbreaks are associated with consuming contaminated food, water, fruits, and vegetables.

8.2.1.1 Intestinal protozoa (Table 8.1)

8.2.2 Extraintestinal protozoa

- Free-living amebas
  - Does not need humans as a host, found in soil and water
  - Common genera and diseases they cause in humans are:

Infectious Diseases. https://doi.org/10.1016/B978-0-443-18742-1.00004-X
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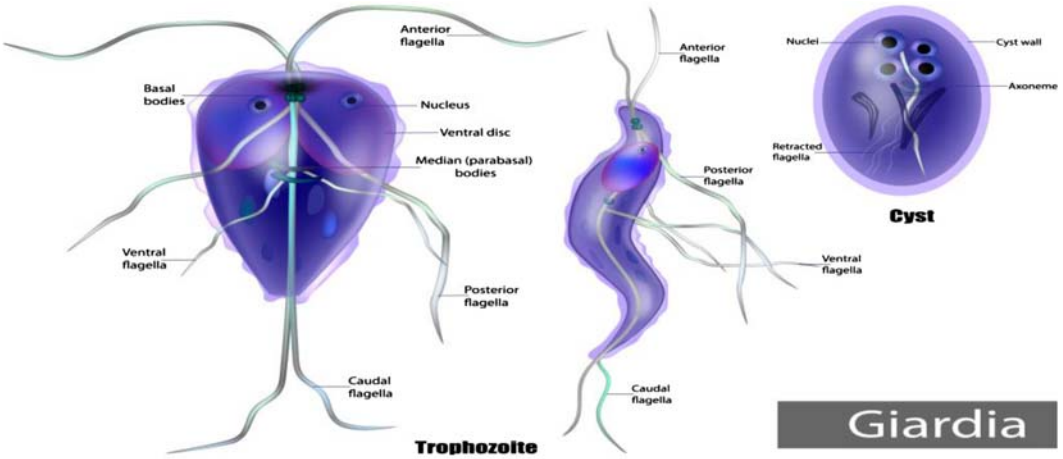

FIGURE 8.1 Giardia.

Table 8.1 Intestinal protozoa, disease, symptoms, and treatment.

Pathogen	Disease	Symptoms	Diagnosis	Treatment
Cryptosporidium	Cryptosporidiosis	Watery diarrhea	Antigen in stool, PCR	Nitazoxanide if symptoms persists
	Drinking infected water and recreational water	Abd cramp, ± fever, and malaise		For AIDS patients HAART
Cyclospora Cayetanensis	Cyclosporiasis	Watery diarrhea, n/v, fever, abd cramps, and wt. lose	Oocysts in stool Intestinal biopsy parasite DNA in stool	SMZ/TMP
Entamoeba Histolytica	Amebiasis	Mild diarrhea to severe dysentery with blood Liver abscess	Fecal exam (require 3–6 stools). Serology Abd CT	Metronidazole or tinidazole followed by paromomycin or iodoquinol for cyst clearance
Giardia Duodenalis	Giardiasis	Foul smelling Greasy diarrhea due to malabsorption of fat	Fecal exam Immunoassay	Metronidazole tinidazole

Abd, abdomen; wt, weight; n/v, nausea and vomiting; SMZ-TMP, Sulfamethoxazole-Trimethoprim.

8.2.2.1 Acanthamoeba and Balamuthis mandrillaris

- Both Acanthamoeba and *Balamuthis mandrillaris* are free-living ameba. Acanthamoeba cause amebic keratitis and chronic (granulomatous) meningoencephalitis, while *Balamuthis mandrillaris* mostly cause chronic meningoencephalitis.

- The ameba is found in water and soil worldwide and infect human through contact lenses, cuts, or skin wounds.
- Life cycle (Fig. 8.2):

8.2.2.1.1 Amebic keratitis (**Also see Section 9.12.6**)

- Typically infects contact lens wearer who wears uncleaned lenses or wears it during swimming.
- Signs and symptoms: Severe pain, redness, foreign body sensation, photosensitivity, and excessive tearing.
- Diagnosis: Examination of Giemsa or trichrome-stained corneal scraping and culture. Initially, corneal ulcer looks like herpes simplex virus (HSV) infection. Later it appears as a stromal ring-shaped infiltrate.
- Treatment:
  - Very difficult to treat and may result in loss of vision
  - Topical chlorhexidine and or polyhexamethylene biguanide
  - Corneal debridement

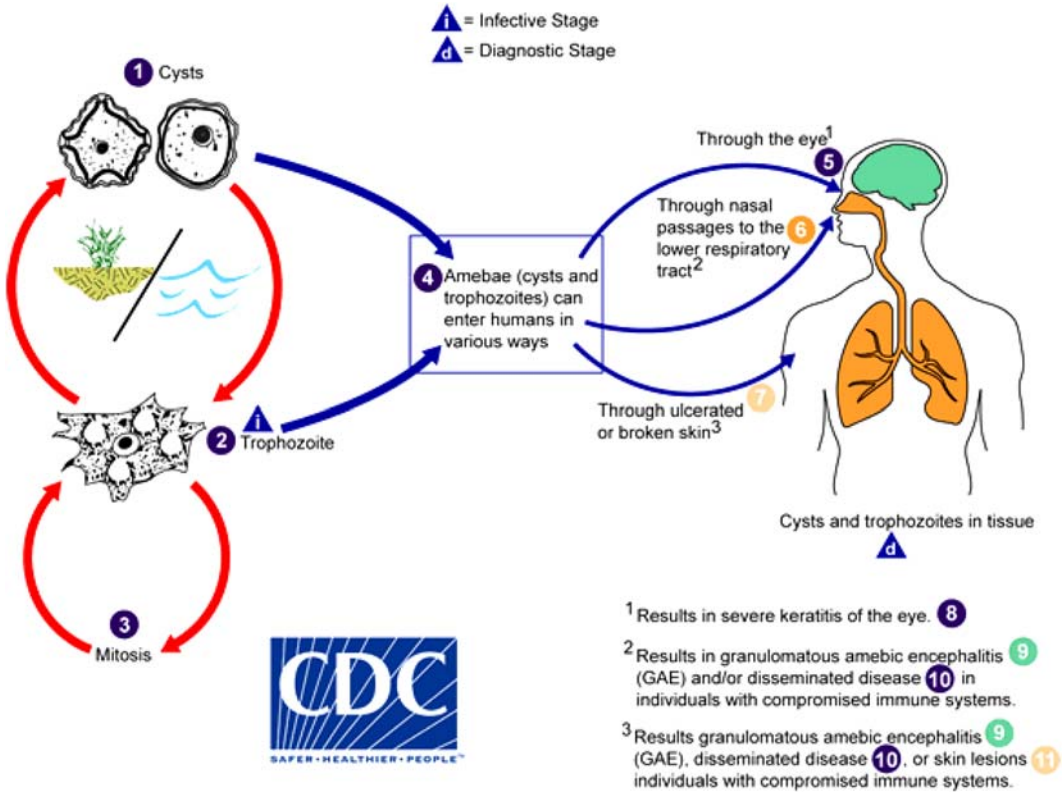
i = Infective Stage
d = Diagnostic Stage
1 Cysts
2 Trophozoite
3 Mitosis
4 Amebae (cysts and trophozoites) can enter humans in various ways
Through the eye[1]
5
Through nasal passages to the 6 lower respiratory tract[2]
Through ulcerated or broken skin[3]
7
Cysts and trophozoites in tissue
d
CDC
SAFER • HEALTHIER • PEOPLE
[1] Results in severe keratitis of the eye. 8
[2] Results in granulomatous amebic encephalitis 9 (GAE) and/or disseminated disease 10 in individuals with compromised immune systems.
[3] Results granulomatous amebic encephalitis 9 (GAE), disseminated disease 10, or skin lesions 11 individuals with compromised immune systems.

FIGURE 8.2 Life cycle of acanthamoeba.

8.2.2.1.2 Chronic meningoencephalitis

- Rare infection caused by Acanthamoeba in immunocompromised patients and by *Balamuthia mandrillaris* in immunocompetent patients.
- Sign and symptoms: Usually insidious onset. Some people develop skin lesions before neurological symptoms develop. Headache, seizure, and mental status change are common symptoms patients experienced.
- Diagnosis:
  - Heat computed tomography (CT) or magnetic resonance imaging (MRI) with contrast → single or multiple rings enhancing lesions in temporal and or parietal lobes.
  - Cerebrospinal fluid (CSF) analysis → ↑white blood count (WBC) mostly lymphocytes, may see trophozoites.
  - Biopsy of skin lesions → amebas can be seen in lesions.
  - Polymerase chain reaction (PCR)
- Treatment:
  - Infection is usually fetal even with treatment.
  - Contact CDC immediately for guidelines of treatment.
  - Miltefosine plus a combination of pentamidine, sulfadiazine, TMP-SMX, or azithromycin is used.

8.2.2.2 Naegleria fowleri

- *Naegleria fowleri* (NF) belongs to the genus Percolozoa and is a free-living freshwater ameba. Also called brain-eating ameba.
- NF grows well at a temperature as high as 45°C. It has three stages of life cycle. Cyst, trophozoites, and flagellates. Trophozoites are the reproductive form and cause invasive diseases in humans. Trophozoites can switch to flagellate form and to cyst form in a stressful environment.
- NF enters the central nervous system (CNS) via nasal mucosa when people swim in contaminated water. People also become infected after using neti pot with contaminated water.
- Once inside the nasal mucosa, ameba enters into respiratory epithelial cells and then migrate into the CNS through the cribriform plates.
- NF has several virulent factors, such as protein Nfa1, nitric oxide formation, and pore-forming protein.
- Ameba ingests brain cells and secrets cytolytic enzymes, which cause intensive damage to brain parenchyma.
- Responsible for the primary (acute) amebic meningoencephalitis.
- Signs and symptoms:
  - Incubation period is usually 1–14 days.
  - Symptoms start with fever, change of smell and taste, headache, stiff neck, and altered mental status.
  - Death is followed in one or two weeks due to brain herniation.

- Diagnosis:
  - History of swimming in freshwater
  - Giemsa-stained CSF examination → motile amebic trophozoites can be seen
  - PCR of CSF
  - Culture
- Treatment
  - Combination of several drugs → miltefosine + amphotericin + fluconazole + azithromycin + rifampin
  - Antiseizure and dexamethasone are usually added to the regime.

8.2.2.3 Protozoa babesia

- Babesia belongs to the genus Babesia and is a pear-shaped protozoan. It primarily infects erythrocytes.
- Rodents are the natural reservoir, and deer tick Ixodes is the vector. Tick bite transmits the parasite to humans and other animals. It requires about 36–72 h for a tick to remain attached to the host to transmit the protozoa to host body.
- Northeast and upper Midwest area, New York state, New Jersey, Wisconsin, and Minnesota are the areas of infestation.
- Parasite Babesia enters the blood and infects red blood cells (RBCs) as sporozoites, where it matures, divides, and forms merozoites.
- RBCs ruptured, and merozoites invades other RBCs, repeating the cycle again and again.
- Life cycle (Fig. 8.3):
- Responsible for a disease called Babesiosis.

8.2.2.3.1 Babesiosis

- Sign and symptoms: Similar to malaria, causes fever, chill, headache, myalgia, and hemolytic anemia, ↑liver enzymes.
- Asplenic, acquired immunodeficiency syndrome (AIDS), and old patients develop severe symptoms, which could be fatal.
- Diagnosis:
- Microscopic exam of blood smears → presence of tetrad form differentiates it from plasmodium species.
- PCR
- Treatment:
  - Atovaquone (750 mg q12h) + azithromycin (500 mg × 1 then 250 mg qd) × 10 days.
  - Quinine (600 mg q 6–8h) + clindamycin (600 iv q6h).

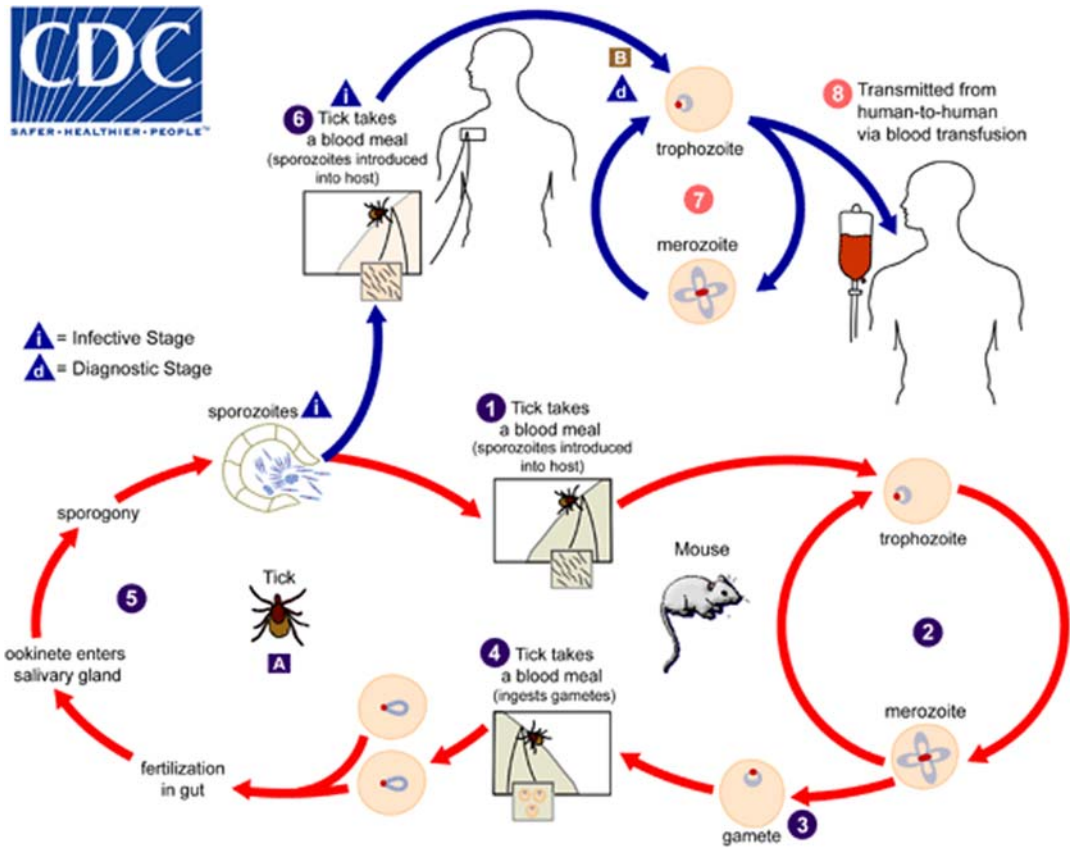

FIGURE 8.3 Life cycle of *Babesia microti*.

8.2.2.4 Trypanosoma cruzi

- Associated with Chagas disease, which is transmitted through the feces of reduviid (kissing) bug. The bug preferably bites on the face and defecates at the site of bite.
- Infection is common in South, Central America, and Mexico.
- *Trypanosoma cruzi* lives as epimastigotes in the lumen of the kissing bug's gut, where it multiples through binary fission and moves around with the help of flagellum. It then transforms into trypomastigote, which is the infected form that invade human cells when the bug bit and defecate at the site. In human cells, it is converted to amastigotes and starts multiplying. Then it converts back to trypomastigotes and bursts out of the cell to infect other cells, and the cycle continues.
- Parasite can be transferred by vertical transmission from mother to fetus leading to congenital Chagas disease.
- Organ transplantation and blood transfusion are also the source of transmission.
- Incubation period is usually up to two weeks.
- Life cycle (Fig. 8.4):

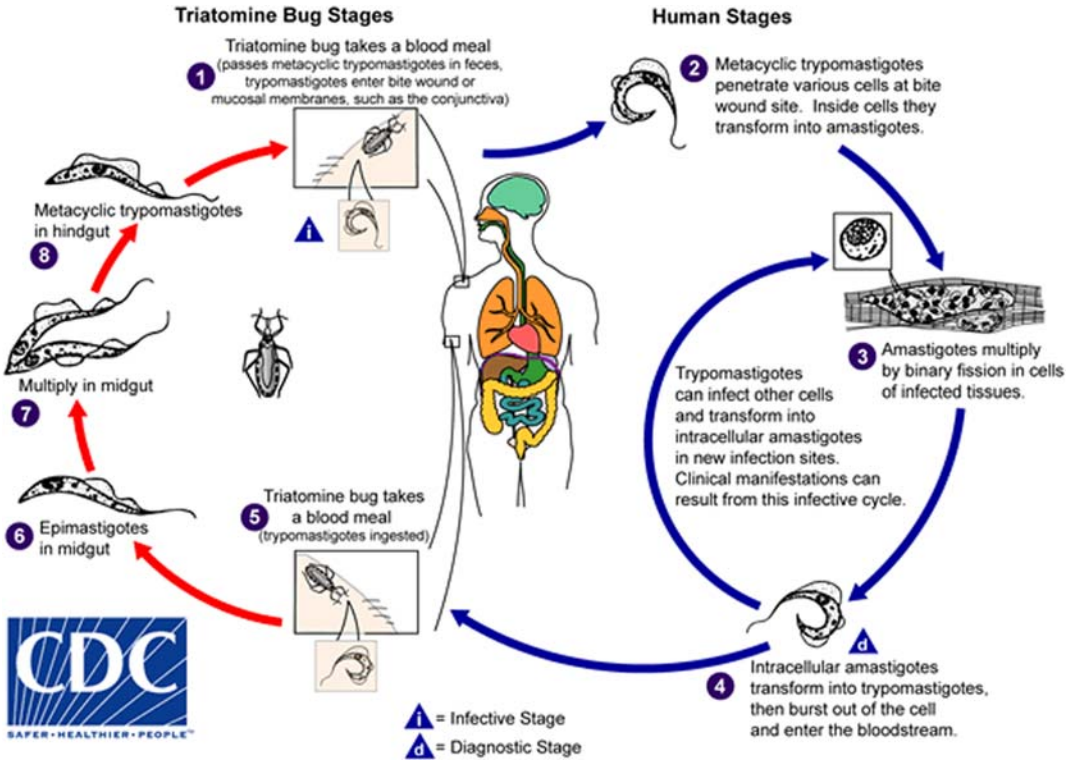
Triatomine Bug Stages
Human Stages
Triatomine bug takes a blood meal
(passes metacyclic trypomastigotes in feces, trypomastigotes enter bite wound or mucosal membranes, such as the conjunctiva)
Metacyclic trypomastigotes penetrate various cells at bite wound site. Inside cells they transform into amastigotes.
Metacyclic trypomastigotes in hindgut
Multiply in midgut
Epimastigotes in midgut
Triatomine bug takes a blood meal
(trypomastigotes ingested)
Amastigotes multiply by binary fission in cells of infected tissues.
Trypomastigotes can infect other cells and transform into intracellular amastigotes in new infection sites. Clinical manifestations can result from this infective cycle.
Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream.
= Infective Stage
= Diagnostic Stage
CDC
SAFER·HEALTHIER·PEOPLE™

FIGURE 8.4 Life cycle of *Trypanosoma cruzi*.

8.2.2.4.1 Chagas disease

- Stages of infection:
  - Acute: Usually asymptomatic, but it could be fatal in some patients. Symptoms start with an erythematous skin lesion at the site of bite or parasite entry called chagoma. If the infection site is conjunctiva, there is unilateral periorbital edema called "Romana sign," which include conjunctivitis and lymphadenopathy. The parasite is engulfed by macrophages, where it survives and multiplies, invading smooth and cardiac muscle cells, neurons, glial cells, and fat cells. Acute phase can last from 8 to 12 weeks.
  - Patients may develop acute myocarditis or meningoencephalitis, especially in immunocompromised patient.
  - Chronic infection can occur 10–20 years after the acute infection. Some people develop chronic Chagas disease without any symptoms. However, about 20%–30% of patients may develop signs of cardiac abnormalities like dilated cardiomyopathy and cardiac block. Gastrointestinal (GI) manifestations like achalasia or Hirschsprung disease, or megacolon.

- Diagnosis:
  - Microscopic exam of blood smears (thin and thick). In the acute phase, trypanosomes can be seen in blood smears, but in the chronic phase, it is rarely seen in peripheral smears.
  - Biopsy of lymph nodes or heart tissue
  - Serological tests
  - PCR
  - Other tests need to be performed in case of suspected Chagas disease are:
    - ➢ Electrocardiogram (ECG)
    - ➢ Echocardiography
    - ➢ Chest X-ray
    - ➢ GI contrast studies or endoscopy for GI symptoms
- Treatment:
  - Benznidazole (5–7 mg/kg/day) or nifurtimox (8–10 mg/kg/day)
    - ➢ Drug is effective in the acute phase and is recommended for if patient ages between 18 and 50. As the age of the patient increases, side effect increases. Treatment is not very effective in the chronic phase. Supportive measures are usually recommended in chronic stage.

8.2.2.5 Trypanosoma brucei

- Cause African trypanosomiasis. Also known as sleeping sickness. It is universally fatal if not treated.
- Transmitted (vector) via the bite of a tsetse fly.
- Inside the human, the parasite rapidly divides, grows, and infects bloodstream, lymphatics, CNC, and almost every organ in the body.
- *Trypanosoma brucei* is endemic in some parts of Africa. It has two subspecies. *T. b. gambiense* is endemic to western sub-Saharan Africa, while *T. b. rhodesience* is in eastern sub-Saharan Africa.
- Life cycle (Fig. 8.5):

8.2.2.5.1 African trypanosomiasis (sleeping sickness)

- Sign and symptoms:
  - Painful erythematous papule at the site of the bite. Over a period of weeks to months, patient develops intermittent fever, headache, muscles and joint pain, facial swelling, and generalized lymphadenopathy (Winterbottom's sign → enlarged posterior cervical lymph nodes triangle)
  - After months to several years, patients develop CNS symptoms such as headache, personality change, somnolence, tremor, ataxia, and coma
- Diagnosis:
  - Microscopic examination of blood smears and CSF

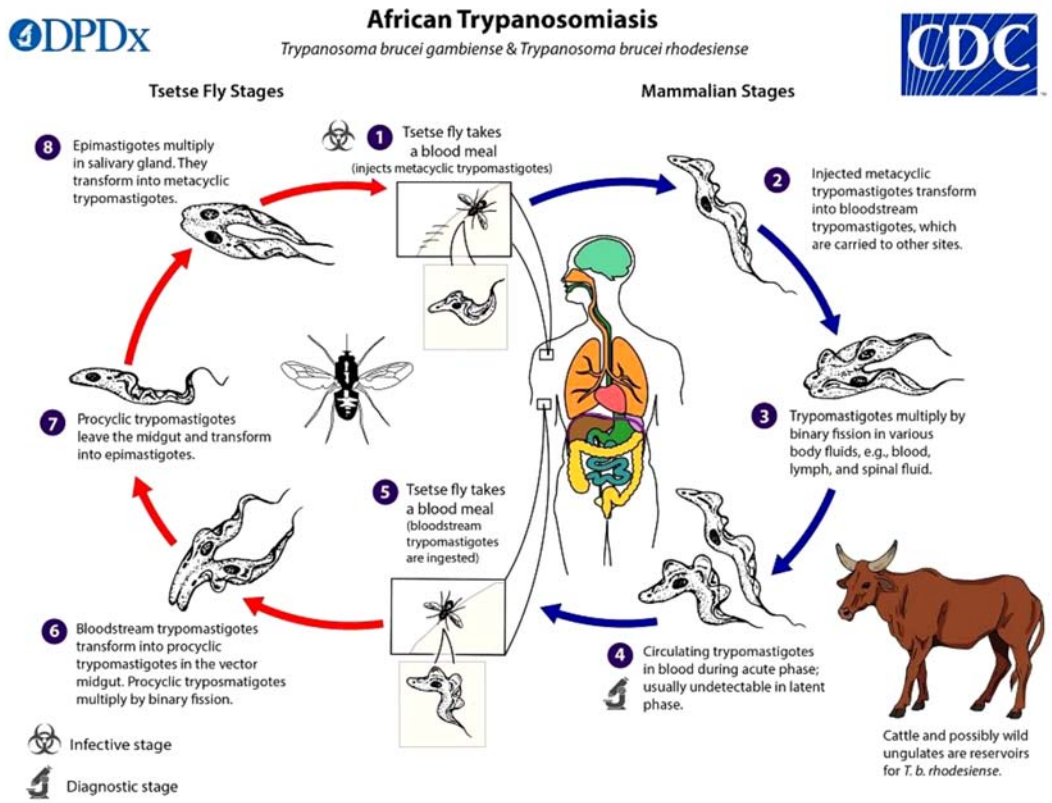
DPDx
African Trypanosomiasis
Trypanosoma brucei gambiense & Trypanosoma brucei rhodesiense
CDC
Tsetse Fly Stages
Mammalian Stages
1 Tsetse fly takes a blood meal (injects metacyclic trypomastigotes)
2 Injected metacyclic trypomastigotes transform into bloodstream trypomastigotes, which are carried to other sites.
3 Trypomastigotes multiply by binary fission in various body fluids, e.g., blood, lymph, and spinal fluid.
4 Circulating trypomastigotes in blood during acute phase; usually undetectable in latent phase.
5 Tsetse fly takes a blood meal (bloodstream trypomastigotes are ingested)
6 Bloodstream trypomastigotes transform into procyclic trypomastigotes in the vector midgut. Procyclic tryposmatigotes multiply by binary fission.
7 Procyclic trypomastigotes leave the midgut and transform into epimastigotes.
8 Epimastigotes multiply in salivary gland. They transform into metacyclic trypomastigotes.
Cattle and possibly wild ungulates are reservoirs for T. b. rhodesiense.
Infective stage
Diagnostic stage

FIGURE 8.5 Life cycle of *Trypanosoma brucei*.

- Treatment:
  - Pentamidine for *T. b. gamdiense* } No involvement of CNS
  - Suramin for *T.b. rhodesience* }
  - Eflornithine or melarsoprol for *T.b. gambiense* }
  - Melarsoprol for *T.b. rhodesience* } CNS involvement

8.2.2.6 Leishmania *sp.*

- Cause leishmaniasis
- Protozoa Leishmania species belong to a family of Trypanosomatidae. There are several subspecies.

- The Leishmania species have two stages of development, amastigote, and promastigote. Promastigote is the infectious form that is transmitted to humans via the bite of female phlebotomine sandy flies (Fig. 8.6).
- Present in various parts of the world, some parts of Asia, the middle east, Africa, and southern Europe, part of Mexico, Central America, and South America.
- Humans, rodents, canines and other animals are reservoirs.

8.2.2.6.1 Leishmaniasis

- Sign and symptoms:
  - Leishmaniasis has three forms of infection: cutaneous, mucosal, and visceral leishmaniasis.
  - **Cutaneous leishmaniasis**: Most common. Painless well-demarcated, erythematous border lesion is developed at the site of the sandy fly's bite. The sore typically develops within a few weeks or months of the sand fly bite. After several months or years, lesion heals itself, but in rare cases, may develop into a nodular skin lesion similar to lepromatous leprosy.
  - **Mucosal leishmaniasis**: Not very common. Parasites spread from the skin to the mucosal membrane and cause sores. Most commonly, the nose is affected, but mouth or throat may also be involved. The onset of mucosal symptoms usually occurs in two years after the resolution of cutaneous lesions.
  - **Visceral leishmaniasis**: Also known as kala-azar. Several weeks or months after the initial skin infection patient developed irregular fever, enlarged liver, pancytopenia, and polyclonal hypergammaglobulinemia.
  - Death will result in patients with progressive disease.
- Diagnosis:
  - Microscopic exam of tissue samples or aspirates
  - Culture
  - PCR
  - Leishmanin skin test → for cutaneous and mucosal infection only
  - Serological tests
- Treatment:
  - Paromomycin (app bid x 10 days)→ Cutaneous infection
  - Liposomal amphotericin IV (3 mg /kg daily x 5 days)] Systemic
  - Miltefosine oral (various)] infection

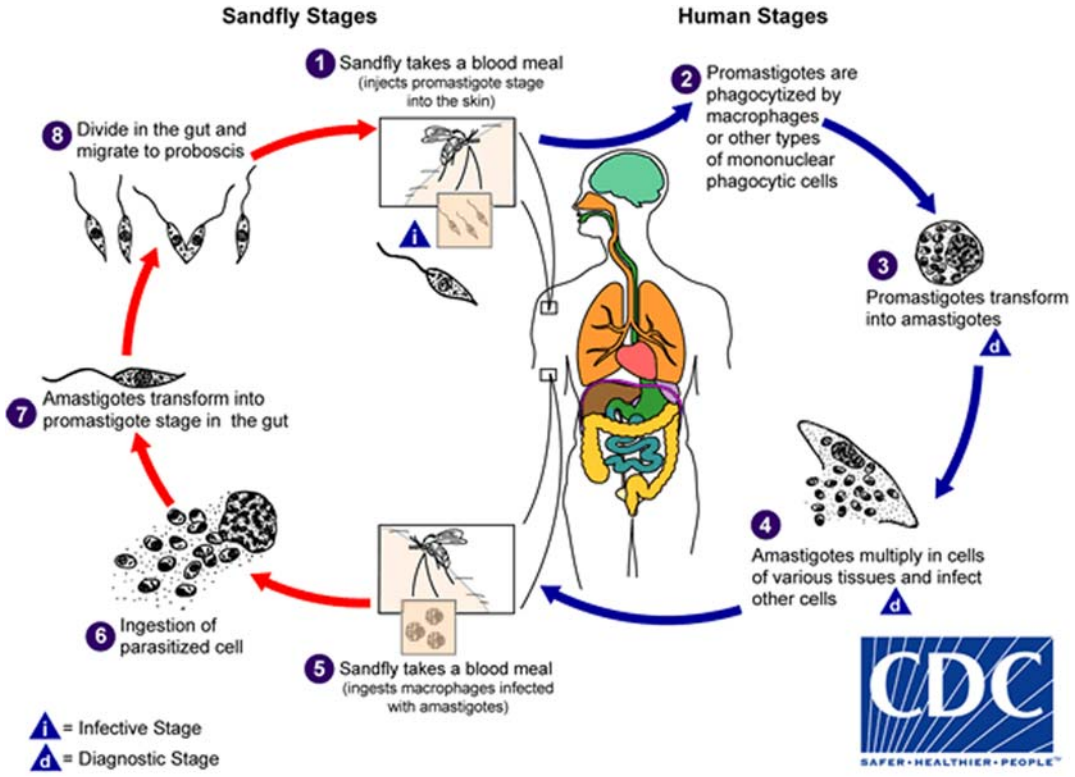

FIGURE 8.6 Life cycle of leishmania.

8.2.2.7 *Plasmodium species*

- Cause malaria
- Transmitted through the bite of female mosquito Anopheles and can also be transmitted by blood transfusion or bite of an infected animal to human (*Plasmodium knowlesi*)
- Present globally, mostly in Asia, Africa, and South America
- There are more than 100 species, but five are involved in human infections
  - *Plasmodium falciparum* → cause the most severe form of malaria
  - *Plasmodium vivax* → use Duffy antigen on RBC to enter in the cell. Patients with sickle cell anemia do not have this antigen, so they are immune to *P. vivax* malaria
  - *Plasmodium malariae*
  - *Plasmodium ovale*
  - *P. knowlesi*

8.2.2.7.1 Life cycle (Fig. 8.7)

When female mosquito bites, it transfers sporozoites (infected form) into human blood, where it immediately reaches to liver cells. In liver cells, they develop into schizonts and burst out from liver cells. Now they are called merozoites. They infect RBC and divide asexually into mature schizonts or trophozoites. Schizonts rupture and release merozoites again and destroy RBC during the process. Some trophozoites differentiate into gametocytes and reach to female mosquito's stomach when mosquitos suck the blood of infected person. Here sexual lifecycle takes place. In the case of *P. vivax* and *P. ovale*, exoerythrocytic phase remains dormant as hypnozoites in the liver for months to years and causes reinfection.

Malaria caused by blood transfusion or sharing contaminated needles does not cause hepatic stage and no delayed recurrences.

Malarial paroxysm: Rupture of RBC and release of merozoites and malarial antigen result in body inflammatory responses, which are manifested as chills, high fever, malaise, headache, and rapid pulse. Fever decreases after 4–6 h. Relapse of paroxysm varies depending upon the plasmodium species.

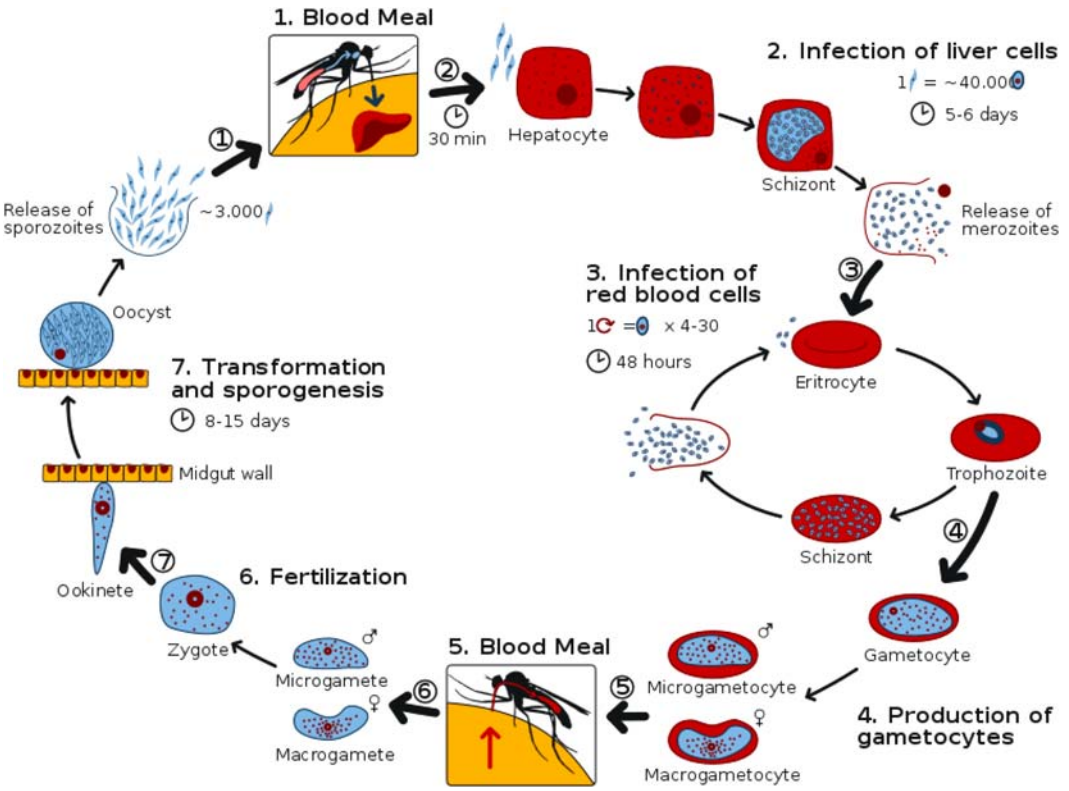

FIGURE 8.7 Malaria life cycle. *Wikipedia commons/CDC.*

- *P. malariae* → fever reappears every 72 h.
- *P. vivax and ovale* → fever reappears every 48 h.
- *P. knowlesi* → fever reappears every 24 h.
- *P. falciparum* → varies, fever can happen every day or every other day.

Signs and symptoms:

- Fever, chill, headache, and malaise
- Anemia, jaundice, and hepatosplenomegaly
- *P. falciparum* causes most severe symptoms, increased morbidity, and mortality →obstruction of blood vessels → end organs damage, acute respiratory syndrome, bleeding, seizure, shock, coma, and death

Diagnosis:

- Light microscopic exam → thin and thick smears
- Thin smears are used to identify malarial species, while thick smears are used to detect infection/parasitemia
- Rapid Plasmodium antigen tests
- PCR

Treatment:

- Based on the severity and Plasmodium species
- IV artesunate for severe malaria followed by oral

Atovaquone-proguanil or oral artemether-lumefantrines

- Combination of artemether and lumefantrine is the treatment of choice for uncomplicated malaria
- Chloroquine can be used for susceptible Plasmodium species
- Chloroquine resistance area: artemether, atovaquone-proguanil, mefloquine, and pyrimethamine/sulfadoxine
- Primaquine kills hypnozoites in liver
- Check glucose-6-phosphate dehydrogenase deficiency before giving chloroquine, primaquine, quinine, tafenoquine as it may cause hemolysis in these patients
- Pregnancy: Artemether-lumefantrine, quinine sulfate + clindamycin
- Prophylaxis: Chloroquine only in chloroquine sensitive area, atovaquone-proguanil, doxycycline, mefloquine, and tafenoquine in all other areas

8.2.2.7.2 Parasites infect blood

- Plasmodium sp → infect RBC
- Trypanosoma → found in blood but do not infect RBC
- Leishmania → found in blood but have amastigotes within macrophages
  Babesia → similar to malaria and does infect RBC but more common in the northeastern part of the United States

8.2.2.8 Trichomonas: also see Section 9.16.3.1

- Motile protozoa with a size of WBCs. It has four or more flagella that provide motility.
- *Trichomonas vaginalis* is the most common protozoal infection in the United States. It is considered a sexually transmitted disease.
- Infect female vagina and male urethra.
- Trichomoniasis is most common among women of ages 40–49.
- Secret cytotoxic proteins that destroy epithelial lining and increase vaginal PH.
- Risk factors:
  - Multiple sexual partners
  - Unsafe sex
  - IV drugs user
  - History of STD
- Sign and symptoms:
  - Vaginal pruritus, burning during urination, frothy malodorous vaginal discharge, redness or soreness of the genitals.
  - Pregnant women are more likely to have their baby early delivery and low birth weight.
  - Males are usually asymptomatic carriers or have mild symptoms of urethritis and milky discharge. It may result in prostate infection.
- Diagnosis:
  - Wet mount preparation on a glass slide and microscopic examination → motile parasite can be seen.
  - NAAT
- Treatment:
  - Metronidazole 1 gm × 1 for the patient and partner.

8.2.2.9 Toxoplasma gondii

- Cause toxoplasmosis
- Main source of infection in humans are cat feces or eating undercooked meats contaminated with cysts
- Cats and cat relatives are the definitive hosts. Cats shed unsporulated oocytes that are transformed into tachyzoites after ingestion. Tachyzoites develop into cyst form, bradyzoites in tissue. Most commonly in skeleton muscles, myocardium, brain, and eyes. These cysts remain there throughout the life of the host (Fig. 8.8)

8.2.2.9.1 Toxoplasmosis

- Sign and symptoms:
  - Infection in an immunocompetent patient is usually mild and self-limited. Patient may have cervical or generalized lymphadenopathy with symptoms similar to mononucleosis.

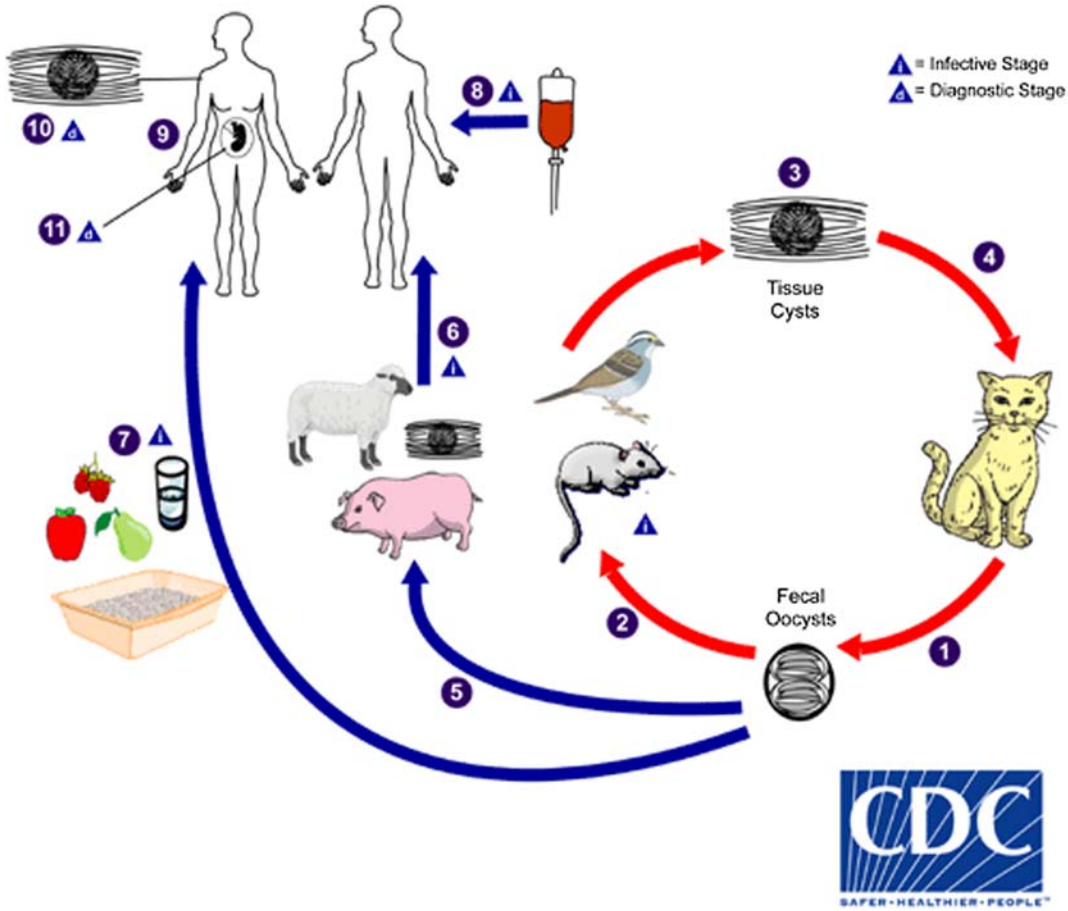

FIGURE 8.8 Life cycle of *toxoplasma gondii*.

- Infection in immunocompromised or AIDS patient commonly infect CNS, eye, less commonly lungs, heart, muscles, and skin.
- Headache, fever, change in mental status, seizure, cranial nerve palsy, and visual abnormalities can be seen in patients with CNS infection.
- Ocular infection usually results from reactivation of congenital infection. Ocular pain, blurred vision, and blindness are common symptoms.
- Pregnancy: Toxoplasmosis is a part of TORCH. Spontaneous abortion, stillbirth, or birth defects may occur if the mother is infected during pregnancy. Women who are infected before pregnancy usually do not transmit the infection to the fetus unless reactivation occurs due to immunosuppression. Chorioretinitis, hydrocephalus, and intracranial calcification are the typical presentation in neonates born from infected mothers during pregnancy.

- Diagnosis:

www.images.google.com see rings enhancing images in MRI or CT.

- Serologic testing → IgM and IgG
- MRI or CT → multiple rings enhancing lesions
- Biopsy → tissue cyst or tachyzoites
- PCR → test for parasite DNA; prefer in pregnancy

- Treatment:
  - Pyrimethamine (200 mg × 1, then 50−75 mg q24h) + sulfadiazine (1−1.5 gm qid) + leucovorin (5−20 mg 3 × /wk).
  - Substitute sulfadiazine to clindamycin (300 mgq8h) or atovaquone (750 mg q12h) in sulfa allergies.
  - Pregnancy: Spiramycin if < 18 weeks gestation. Pyrimethamine-sulfadiazine + leucovorin If > 18 weeks gestation.
  - Sulfamethoxazole—trimethoprim is used prophylactically in AIDS patients with CD4 counts <100 cells/mm^3.

8.3 Microsporidia

- Obligate intracellular parasites, single cell eukaryotic spore-forming parasites thought to be fungi but recently reclassified.
- Microsporidia produce spores that are highly resistant to the environment and are the infective form. Spores have polar tubules or filaments that coiled inside the spores and possess degenerated mitochondria (mitosomes).
- More than 1400 species exist; only 15 cause disease in humans. *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* cause most of the infections in humans.
- Mostly cause symptomatic disease in patients with AIDS or immunocompromised (opportunistic pathogens).
- Presents worldwide.
- Responsible for diarrhea, malabsorption, conjunctivitis, peritonitis, sinusitis, encephalitis, cholecystitis, and cholangitis in immunocompromised patients.
- Transmission
  - Inhalation, ingestion, direct contact, person to person, exposure to swamp water or crop irrigation area.
  - Most of the transmission occurs through food, including fish and crustaceans.
- Diagnosis:
  - Microscopic exam
  - PCR
- Treatment:
  - Albendazole
  - Voriconazole
  - AIDS patients use HAART

8.4 Helminths

- Multicellular organisms. Classified into two major phyla:
  - Nematodes (roundworm)
  - Platyhelminthes (flatworm)

8.4.1 Nematodes (roundworm)

- Nonsegmented round or cylindrical shape with body cavity, complete digestive tract, and separate sexes
- No suckers and no hooks
- Further classified into intestinal and nonintestinal nematode

8.4.1.1 Intestinal nematode

- They mostly stay in the intestine but migrate to the lung in part of their life cycle. Three of them (*Ascaris lumbricoides* (*Fig. 8.9*), *Trichuris trichiura*, and *Enterobius vermicularis* [pinworm]) are acquired by ingestion of eggs, while *Necator americanus* and *Strongyloidiasis stercoralis* are acquired when larvae penetrate through foot skin.
- Food or water contaminated with feces containing eggs are swallowed. In the intestine, eggs are hatched into larvae and burrow through the intestinal wall and reaches the lungs, where they grow. Infected person cough-up the larvae and swallows them. Larvae reach the intestine again, where they mature and produce eggs which pass down into feces and infect others.
- Enterobius and Trichuris do not invade other tissue.

8.4.1.1.1 Ascaris lumbricoides (Fig. 8.10)

- Most common intestinal worm. Approximately one billion people worldwide are infected annually.
- Affect mostly tropical and subtropical countries around the world.
- Average size of the worm is 20–30 cm in length. Adult average life span is one year.
- Source of infection and life cycle:
  - Ingestion of eggs found in contaminated soil, water, and food.
  - Inside the duodenum, eggs are hatched and larvae are released and enter into the circulation, and from circulation it reaches to liver and lungs. When infected people cough, these larvae are expectorated and swallow again and reaches to the small intestine where male and female worms copulate and female produce thousands of eggs daily which are shed to the environment through feces, where they can survive up to 17 months.
- Sign and symptoms:
  - Depends upon the parasitic load. If the load is low, people might be asymptomatic. Most common symptoms are abdominal cramps or pain, nausea, or

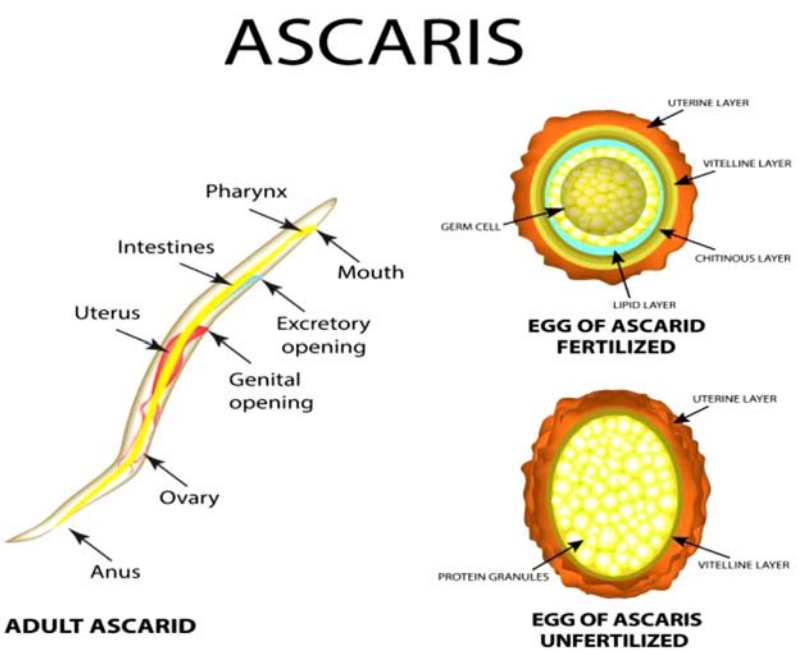

FIGURE 8.9 Adult ascaris with egg.

vomiting. Obstruction of pancreatic or bile duct may cause pancreatitis or cholangitis. Cough, wheezing, and hemoptysis while larvae are in the lungs. Malnutrition in children.

- Diagnosis:
  - Microscopic exam of stool → eggs or adult worms
  - Eosinophilia
  - Proctoscopy or colonoscopy
- Treatment:
  - Albendazole 400 mg × 1
  - Mebendazole 100 mg twice daily × 3 days
  - Ivermectin 200 ug/kg/day × 2 days
  - In pregnancy piperazine 50 mg/kg/day × 5 days or pyrantel pamoate 11 mg/kg max 1 gm × 1

8.4.1.1.2 Trichuris trichiuria (Fig. 8.11)

- Also called whipworm due to its shape. The size of the worm is about 3–5 cm. Female worm is larger than male.
- People get infected by fecal–oral route or ingesting eggs from contaminated soils, water supply, or food.
- Eggs hatch in human's small intestine, and larvae move to the cecum, where they penetrate the mucosa and mature into adulthood.

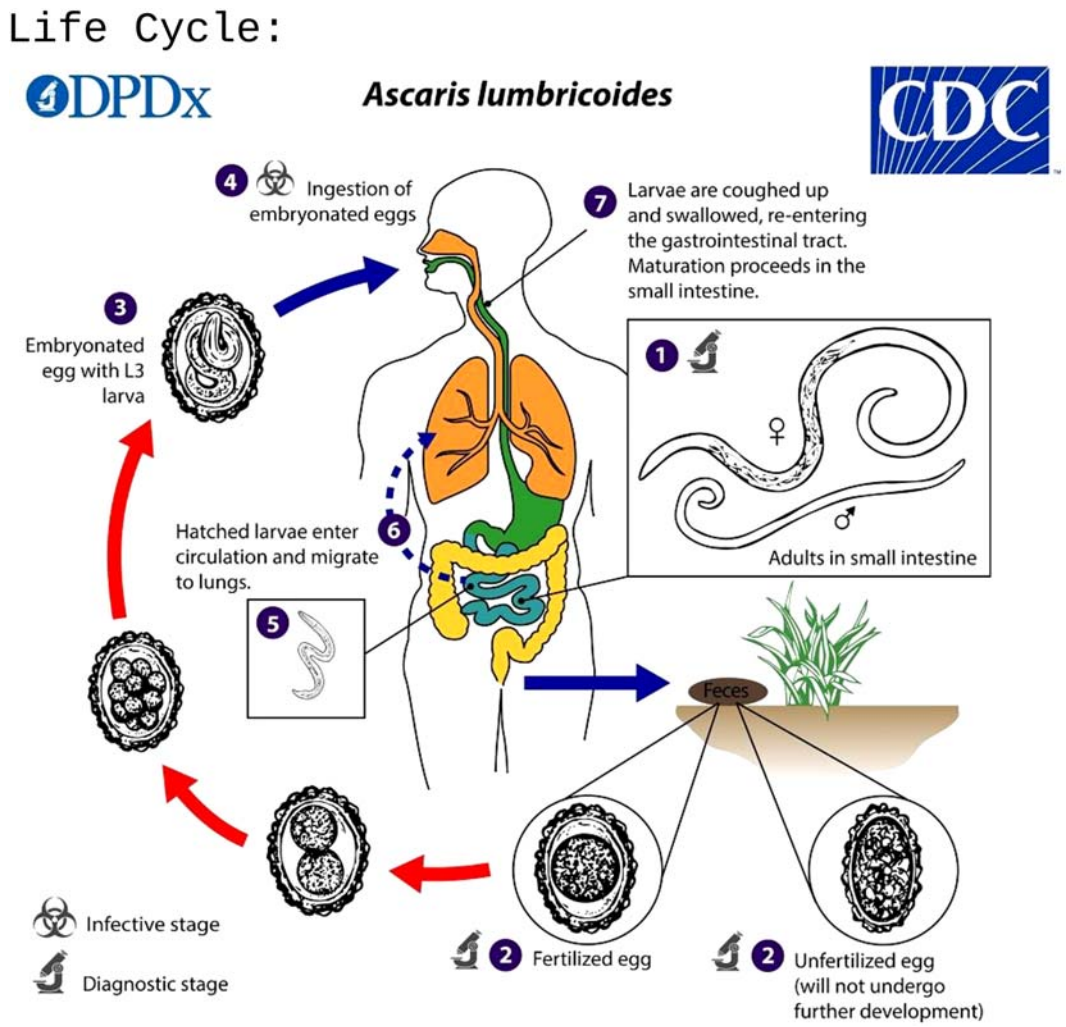

FIGURE 8.10 Life cycle of *Ascaris lumbricoides*.

- The worm lives around 1–4 years before they die.
- Sign and symptoms:
  - Asymptomatic if the parasitic load is low.
  - Abdominal pain, anorexia, weight loss, anemia, and malnutrition.
- Diagnosis:
  - Microscopic exam of stool
  - Proctoscopy or colonoscopy → "coconut cake rectum" from white bodies of the adult worms
  - Complete blood count (CBC)

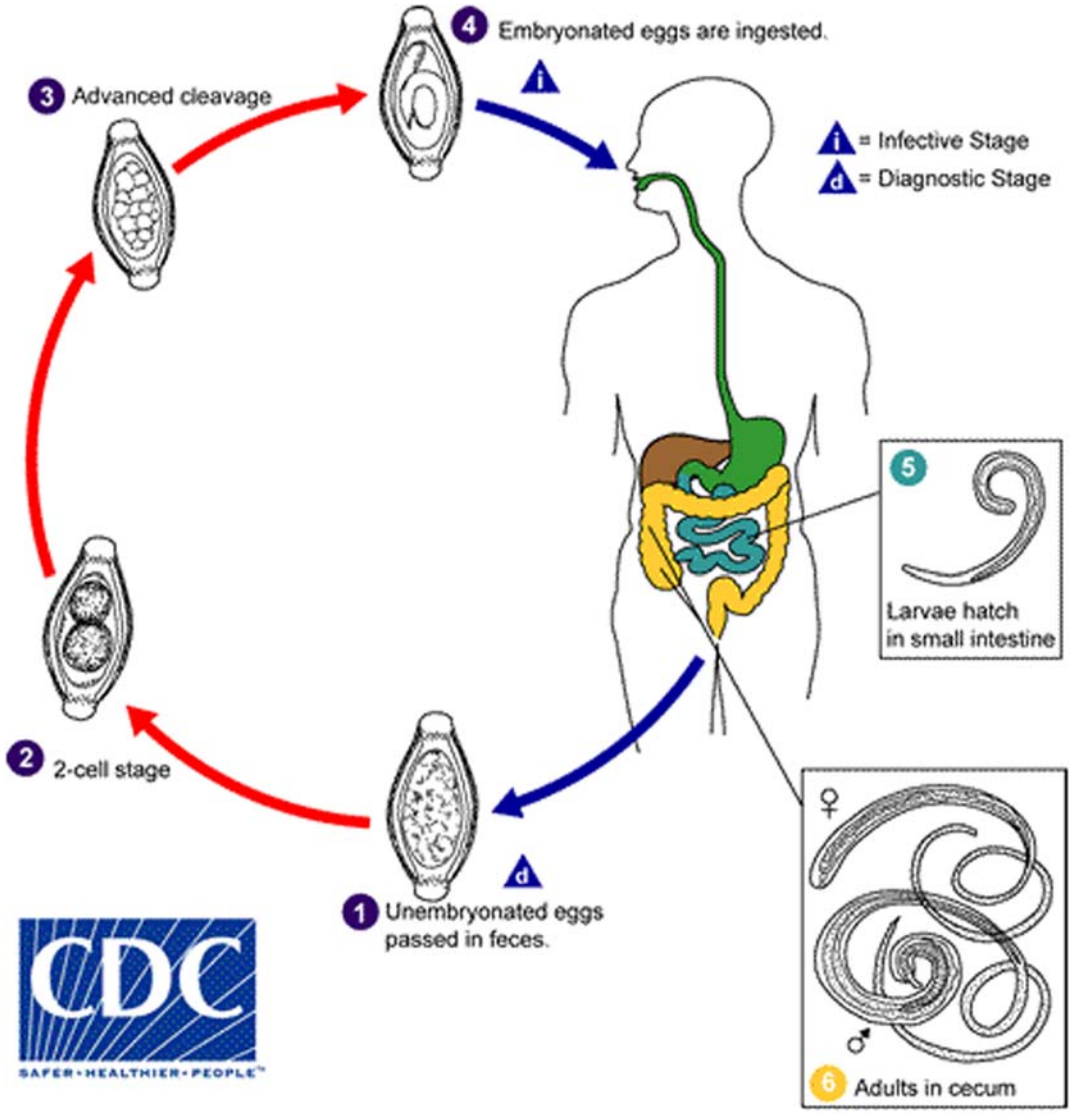

FIGURE 8.11 Life cycle of *Trichuris trichiuria*.

- Treatment
  - Albendazole 400 mg daily × 3 days
  - Mebendazole 100 mg twice daily × 3 days

8.4.1.1.3 Trichinella spiralis

- *Trichinella spiralis* is a roundworm, and it causes trichinellosis.
- People get infected by ingesting raw or undercook meat, usually pork, contaminated with encysted larvae.
- Present worldwide and cause approximately 10,000 cases every year. Highest number of cases are reported in China, where the consumption of pigs is highest.
- Worm form cyst of size 1.2–2.2 mm in skeleton muscles. When humans ingest contaminated raw or undercooked meat, under the effects of digestive enzymes, larvae are released and invade the small intestine. Here larvae turn into adults, and male and female worm mate. Female produce larvae and these larvae enter into

lymphatic circulation and reach to skeleton muscles, brain, and myocardium, where they encyst (Fig. 8.12).

- Sign and symptoms:
  - Abdominal pain, diarrhea, fever, muscles pain, periorbital edema, eosinophilia, weakness, fatigue, conjunctivitis and subconjunctival hemorrhage, headache, cough, arrhythmia, meningitis, encephalitis, hematuria, and renal failure.
- Diagnosis:
  - Serological testing
  - Muscles biopsy
  - CBC
  - ECG

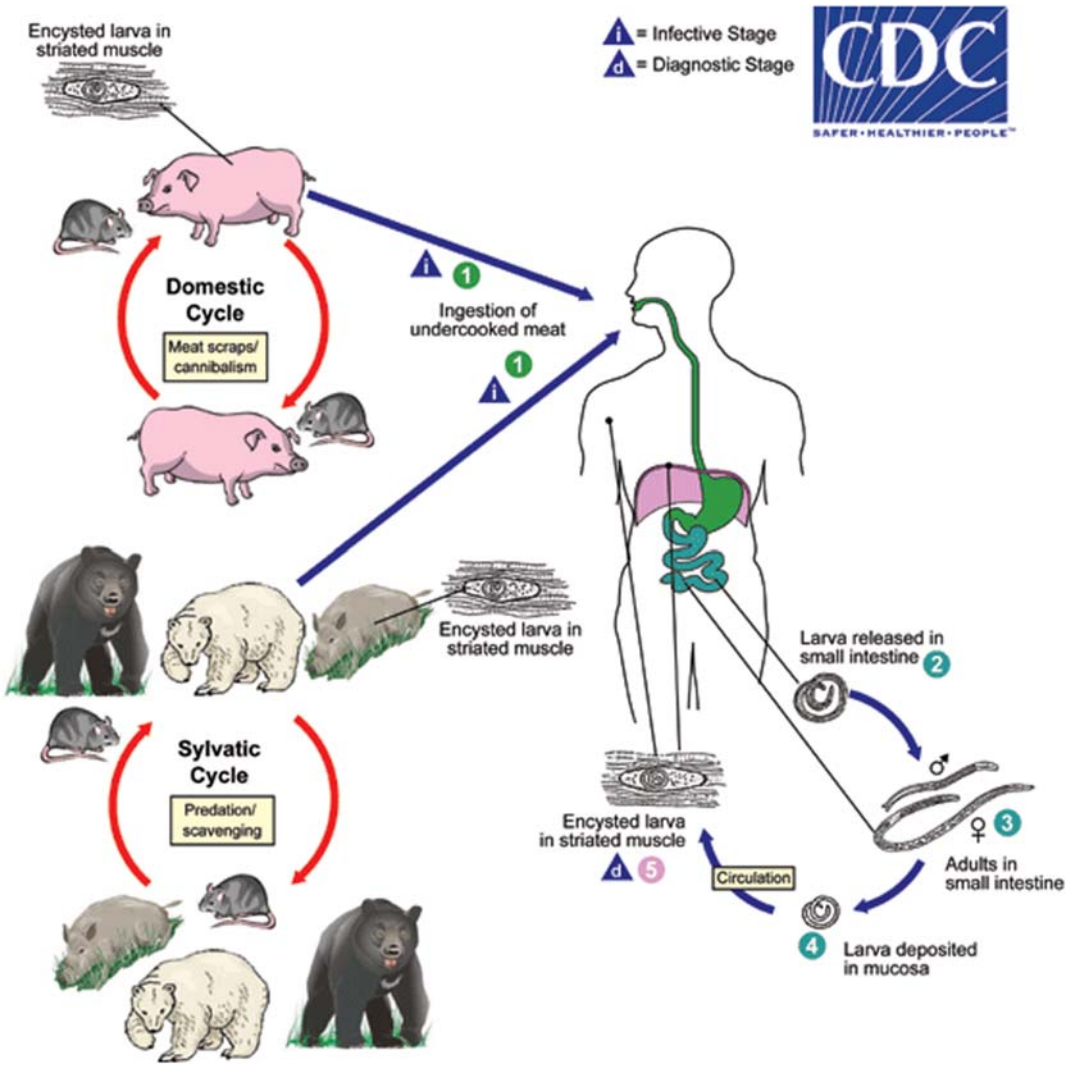

FIGURE 8.12 Life cycle of *trichinella spiralis*.

- Treatment:
  - Albendazole 400 mg twice daily × 14 days
  - Mebendazole 100 mg twice daily × 3 day

8.4.1.1.4 Enterobius vermicularis

- Most common helminth infection worldwide and mostly affects children.
- Also called pinworm as the female worm has pin-like tail. Humans are the only natural host.
- Children get infected by direct contact with the infected person, ingestion of eggs via contaminated utensils, fecal oral route, and using infected fomites.
- Ingested eggs in human small intestine develop into adult worms. Female worms and ova migrate to the anal area mainly at night and deposit thousands of eggs. This migration causes intense pruritis. Scratching the anal area results in contamination of the fingers. If hands are not washed thoroughly, the eggs are ingested, and the cycle keeps repeating (Fig. 8.13).
- Sign and symptoms:
  - Perianal pruritis
  - Appendicitis if the worm blocks the lumen of the appendix
- Diagnosis:
  - Examination of perianal area for worm or ova
  - Microscopic exam on cellophane tape
- Treatment:
  - Mebendazole 100 mg × 1 dose, repeat in 2 weeks
  - Albendazole 400 mg × 1 dose, repeat in 2 weeks
  - Pyrantel pamoate 11 mg/kg max 1 gm given 2 weeks apart

8.4.1.1.5 Necator americanus (Fig. 8.14)

- Larvae usually 1 cm long, penetrate through the skin, and reach the lungs through the circulatory system.
- They penetrate the alveoli and reach to pharynx via the bronchial tree.
- In the pharynx, they are swallowed and reach the small intestine and stay there and become adult worms.
- Signs and symptoms:
  - Rash at the site of entry
  - Abdominal pain, nausea, and anorexia
  - Iron deficiency anemia
  - Cough, wheezing, hemoptysis, and eosinophilia
- Diagnosis:
  - Stool exam
  - CBC, iron level
- Treatment:
  - Albendazole 400 mg/day × 3 days
  - Mebendazole 100 mg twice daily × 3 days
  - Pyrantel pamoate

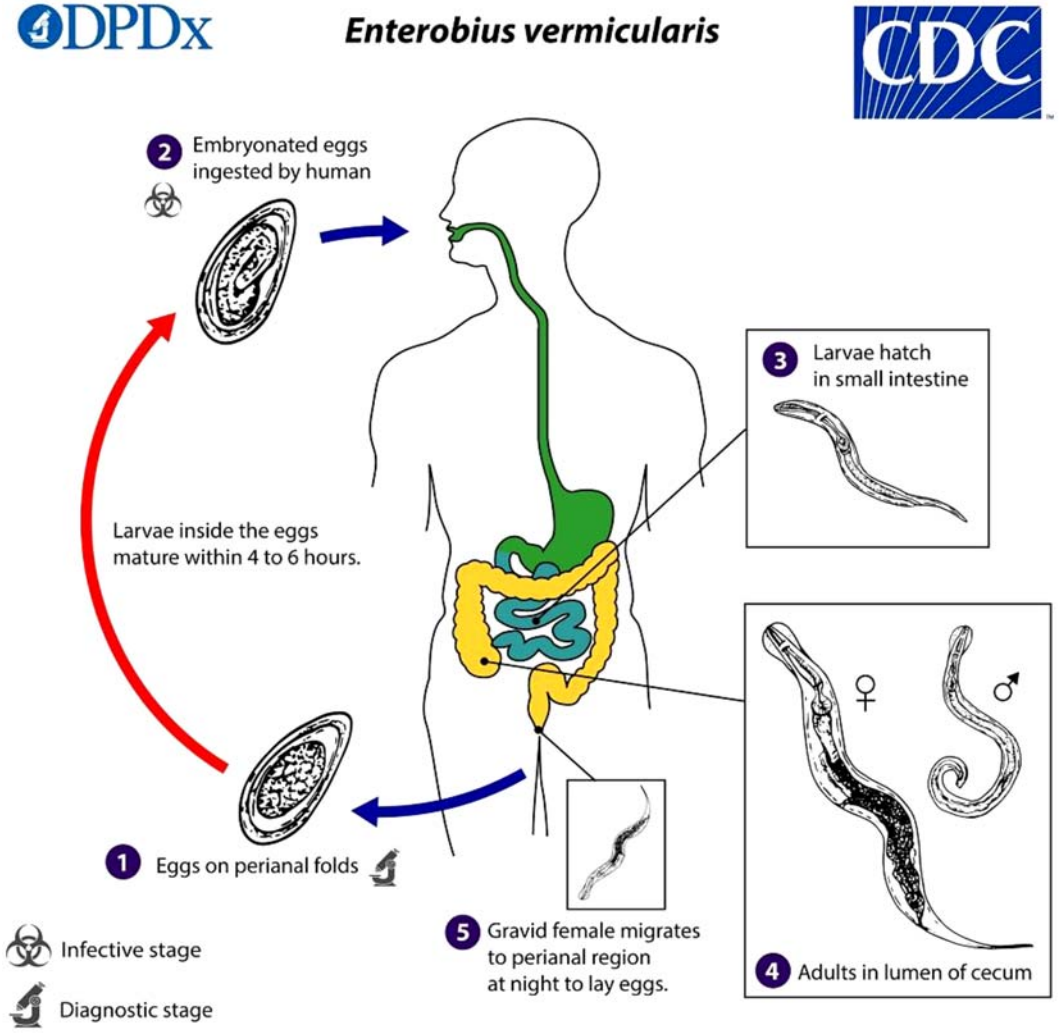
DPDx
Enterobius vermicularis
CDC
2 Embryonated eggs ingested by human
3 Larvae hatch in small intestine
Larvae inside the eggs mature within 4 to 6 hours.
1 Eggs on perianal folds
5 Gravid female migrates to perianal region at night to lay eggs.
4 Adults in lumen of cecum
Infective stage
Diagnostic stage

FIGURE 8.13 Life cycle of *Enterobius vermicularis*.

8.4.1.1.6 Strongyloides stercoralis

- Strongyloides cause life-threatening diseases in humans.
- Present worldwide. Most of the cases are reported in warm, moist area and countries with poor sanitation.
- About 91%–75% of cases are reported in Gabon and Peru, respectively.
- Larvae (filariform), which is the size of approximately 2 mm, penetrate the skin and travel to the lungs, where they mature.
- The mature worms travel up the trachea, swallowed, invade the mucosa of the small intestine and lay eggs.

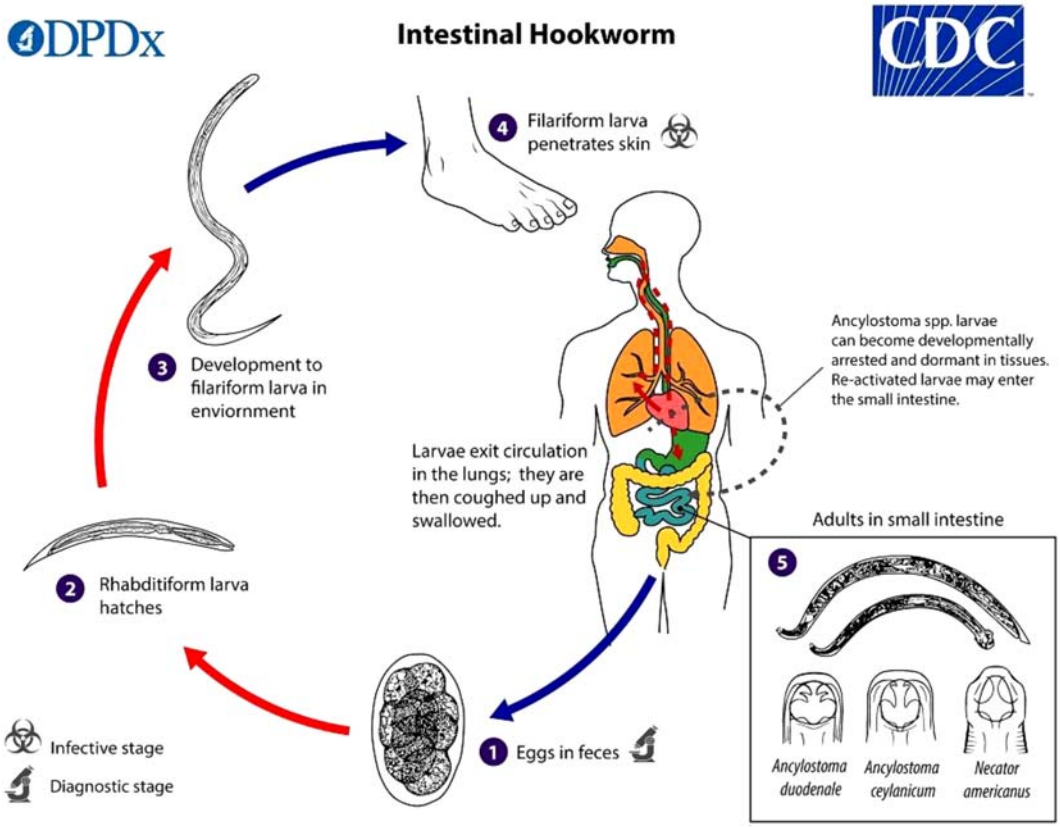
DPDx
Intestinal Hookworm
CDC
4 Filariform larva penetrates skin
3 Development to filariform larva in enviornment
2 Rhabditiform larva hatches
1 Eggs in feces
Infective stage
Diagnostic stage
Larvae exit circulation in the lungs; they are then coughed up and swallowed.
Ancylostoma spp. larvae can become developmentally arrested and dormant in tissues. Re-activated larvae may enter the small intestine.
Adults in small intestine
5
Ancylostoma duodenale
Ancylostoma ceylanicum
Necator americanus

FIGURE 8.14 Life cycle of intestinal hookworm.

- Eggs are hatched to larvae (rhabditiform, which is noninfectious form) and are excreted in faces.
- In soil, rhabditiform larvae mature into filariform larvae, which is the infective form, or mature free-living worm and complete the cycle.
- Some of the rhabditiform larvae inside the intestinal mucosa mature to infective filariform and reinfect the host. This results in autoinfection and have high mortality rate.
- Repeated autoinfection results in the dissemination of larvae to different organs such as the liver and brain.
- Signs and symptoms:
  - Pulmonary symptoms: Cough, wheezing, hemoptysis, and eosinophilia
  - GI symptoms: Abdominal pain, diarrhea, nausea, and vomiting
  - End organ infection: Sepsis, fever, and encephalitis
- Diagnosis:
  - Stool examination → low sensitivity

- Serological tests
- PCR and RT-PCR → gold standard

- Treatment:
  - Ivermectin 200 mg daily × 2 days
  - Albendazole 400 mg bid × 7 days

8.4.1.2 Nonintestinal nematode

8.4.1.2.1 Onchocerca volvulus (Fig. 8.15)

- Cause river blindness.
- Vector → infected black fly of the genus simulium transmits the disease to humans.
- Black fly lives and breeds near rivers and streams, infecting eyes, resulting visual impairment and blindness. Therefore, it is named river blindness disease.
- Larvae inoculate the skin after the fly bites and cause skin nodules, where they develop into the adult worm and live in the nodules for about 15 years
- Female adult worms in subcutaneous nodules produce microfilariae which travel to peripheral blood, urine, sputum, and eyes. In eyes, these microfilariae cause visual disturbance and complete blindness.
- When blackfly bites the infected person, she ingests the larvae, which migrate to fly muscles and develop into infected form and migrate to the fly proboscis, where the parasite is ready to infect other humans when the fly bites again.
- Common in rural agriculture areas in sub-Saharan Africa
- Sign and symptoms
  - Skin nodules (worms live in it), pruritis, atrophy, depigmentation, and adenopathy
  - Keratitis, uveitis, and blindness
- Diagnosis
  - Skin biopsy of nodules and microscopic exam
  - Slit-lamp eye exam → microfilariae visible
  - PCR
- Treatment:
  - Doxycycline 100 mg bid × 6 weeks + ivermectin 150 ug/kg × 1. May repeat ivermectin q3-6 months and then q years × 3 years
  - Doxycycline → kills worm but not microfilariae

* Ivermectin causes a severe reaction if the patient is coinfected with Loa loa.

8.4.1.2.2 Wuchereria bancrofti

- Thread-like worms live in human lymph system and produce microfilariae. Microfilariae circulate in the infected person's blood and infect mosquitos when they bite.
- Inside the mosquito, microfilariae grow and develop into larvae form and transmit back to human when the mosquito bites to another human.

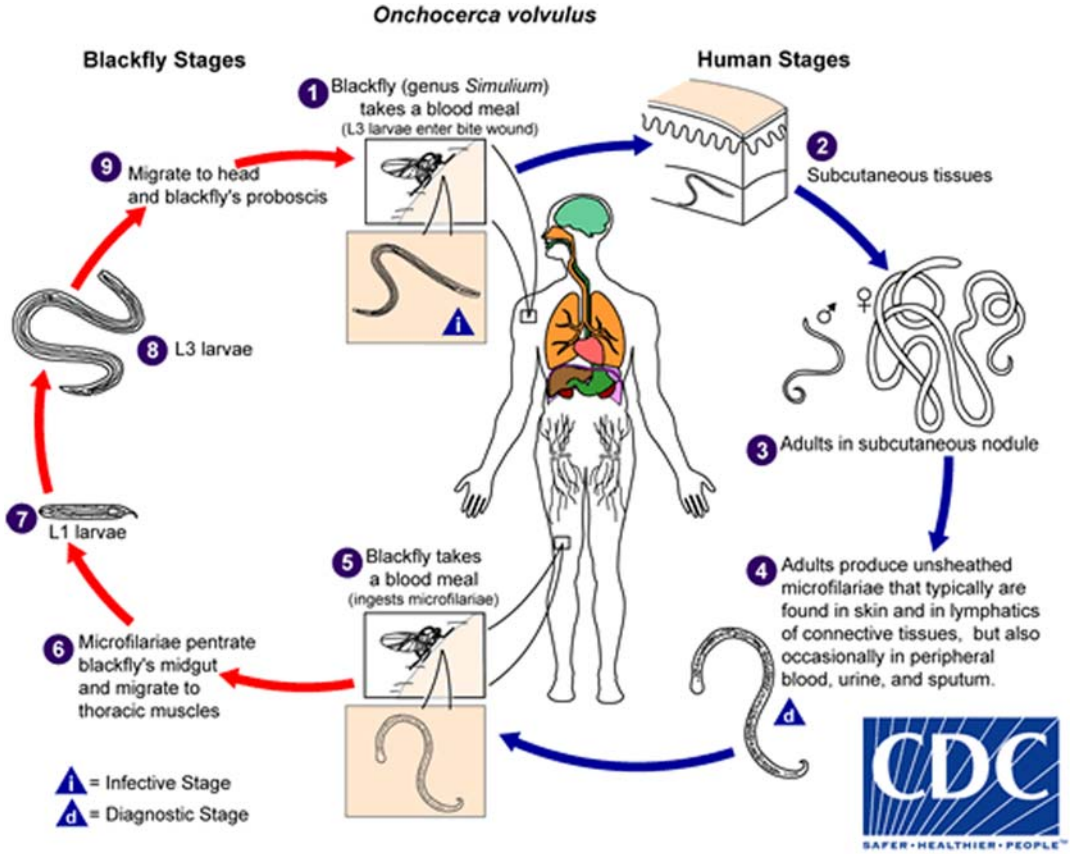
Onchocerca volvulus
Blackfly Stages
Human Stages
1 Blackfly (genus Simulium) takes a blood meal (L3 larvae enter bite wound)
2 Subcutaneous tissues
3 Adults in subcutaneous nodule
4 Adults produce unsheathed microfilariae that typically are found in skin and in lymphatics of connective tissues, but also occasionally in peripheral blood, urine, and sputum.
5 Blackfly takes a blood meal (ingests microfilariae)
6 Microfilariae pentrate blackfly's midgut and migrate to thoracic muscles
7 L1 larvae
8 L3 larvae
9 Migrate to head and blackfly's proboscis
i = Infective Stage
d = Diagnostic Stage
CDC
SAFER·HEALTHIER·PEOPLE™

FIGURE 8.15 Life cycle of *Onchocerca volvulus*.

- Responsible for filarial fever, elephantiasis, and tropical pulmonary eosinophilia.
- Vector →Female mosquito *aedes aegypti* and several other species of mosquitos can transmit microfilariae to humans via bite during a blood meal.
- Average adult life span is 5–7 years.
- Common in Pacific islands, some parts of Africa, Middle east, and South America
- Life cycle (Fig. 8.16):
- Responsible for:
  - Filarial fever
    - Episode of fever with headache and acute adenolymphangitis.
  - Elephantiasis (Chronic filarial disease)
    - Chronic infestation of the lymphatic system by the worms and filariae result in obstruction, destruction, inflammatory response, infections, and lymphedema. This gives the appearance of elephant legs. Men can develop hydrocele or swelling of the scrotum.
  - Tropical pulmonary eosinophilia

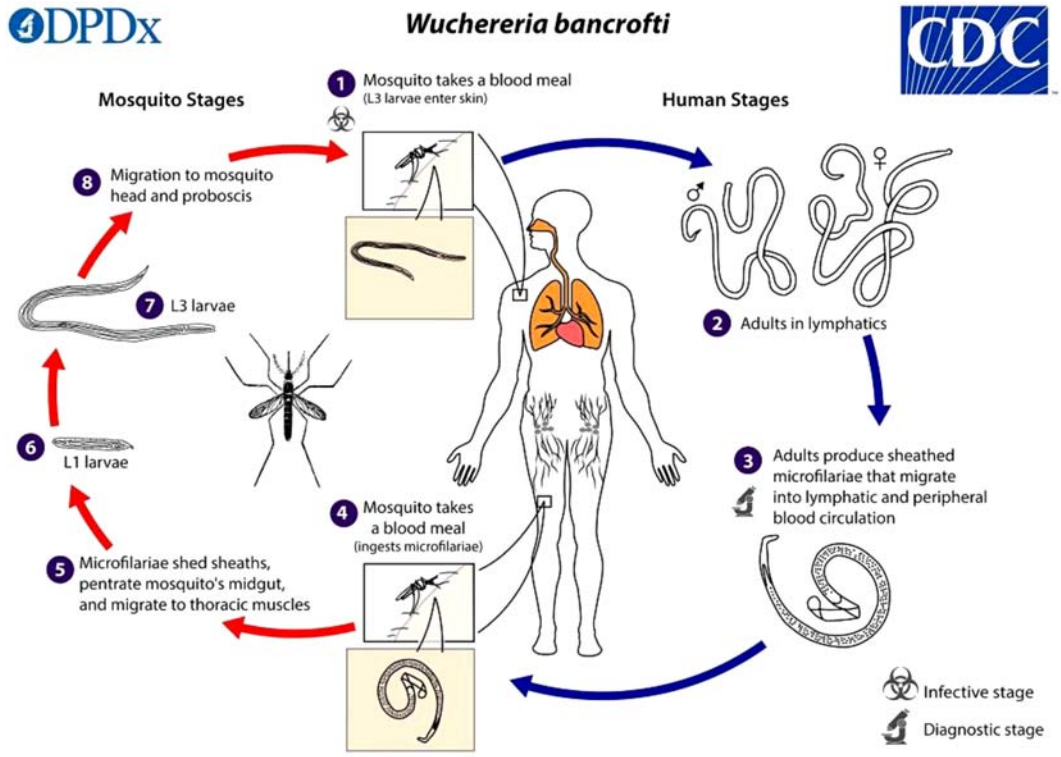
DPDx
Wuchereria bancrofti
CDC
Mosquito Stages
Human Stages
1 Mosquito takes a blood meal
(L3 larvae enter skin)
2 Adults in lymphatics
3 Adults produce sheathed microfilariae that migrate into lymphatic and peripheral blood circulation
4 Mosquito takes a blood meal
(ingests microfilariae)
5 Microfilariae shed sheaths, pentrate mosquito's midgut, and migrate to thoracic muscles
6 L1 larvae
7 L3 larvae
8 Migration to mosquito head and proboscis
Infective stage
Diagnostic stage

FIGURE 8.16 Life cycle of *Wuchereria bancrofti*.

  - Hypersensitivity response to microfilariae results in marked eosinophilia, bronchospasm, lungs infiltrate, low grade fever, and pulmonary fibrosis.
- Diagnosis
  - Microscopic exam of the blood sample drawn at night
  - Adult worm can be visualized in the dilated lymphatic vessels by ultrasound
  - Biopsy
  - Serology tests
  - PCR
- Treatment
  - Diethylcarbamazine (DEC) (6 mg/kg × 1) + doxycycline 200 mg daily × 21 days.
  - Doxycycline → kills the worms but not microfilariae.

8.4.1.2.3 Dracunculus medinensis

- Cause dracunculiasis
- Infection is common in rural and poorer countries such as Chad, South Sudan, Ethiopia, and Mali
- Transmission

  - Drinking water contaminated with microcrustaceans (copepods) that swallow the larvae.
  - The disease can also be spread by eating raw or undercooked fish or frogs that have swallowed the infected copepods.
  - Inside the gut, larvae penetrate the bowel and enter the abdominal cavity, where they grow into adult worms.
  - Adult female worm migrates to subcutaneous tissue and resides there. Painful blisters are form and burst in 24–72 h. Infected peoples go into the water, and worms release immature larvae into the water. Copepods swallow them and a new cycle starts.
- Sign and symptoms:
  - Painful, with intense itching skin lesions which contain adult worm
  - Chronic form result in debilitating arthritis
- Diagnosis
  - Clinical → white, filamentous worm visible at the skin lesion
  - X-ray → calcified worm visible
- Treatment
  - Manual removal
- Life cycle (Fig. 8.17):

8.4.1.2.4 Loa loa

- Cause loiasis
  - Nonpainful swelling of the body commonly near the joints. Comes and goes.
  - Less commonly, itching all over the body, muscle pain, and fatigue.
  - Subconjunctival infestation of adult worm. Physically see crawling of worms in subconjunctival tissue of the eyes.
- Transmission
  - Biting of a deer fly or horse fly
  - Microfilariae grow into adult worms in the subcutaneous tissue and migrate to the conjunctiva of the eye
  - Microfilariae circulate in the blood
- Affected area
  - Western and Central Africa
- Diagnosis
  - Eye exam → shows adult worms
  - Microscopic blood examination shows microfilariae
  - PCR
- Treatment
  - Number of microfilariae <8000/mL → DEC (9 mg/kg in 3 divided dose × 21 days)
  - Number of microfilariae >8000/mL → albendazole 200 mg po bid × 21 days then DEC
- Life cycle (Fig. 8.18):

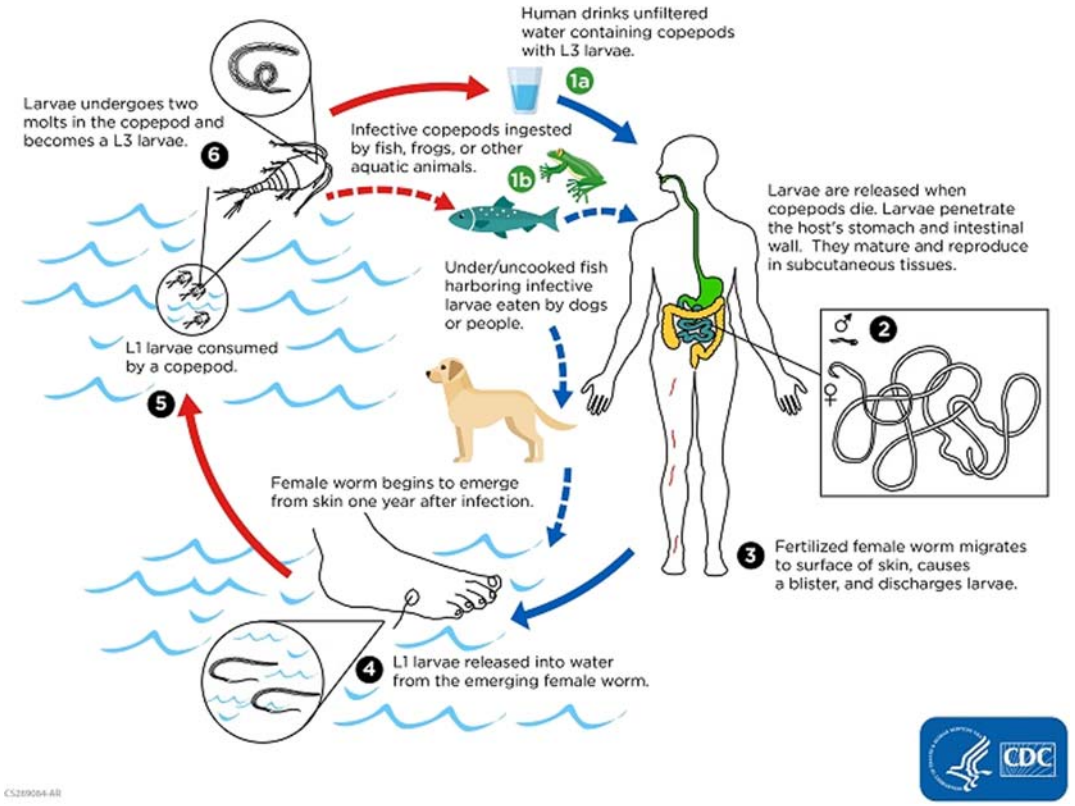
Human drinks unfiltered water containing copepods with L3 larvae.
1a
Infective copepods ingested by fish, frogs, or other aquatic animals.
1b
Larvae undergoes two molts in the copepod and becomes a L3 larvae.
6
Larvae are released when copepods die. Larvae penetrate the host's stomach and intestinal wall. They mature and reproduce in subcutaneous tissues.
Under/uncooked fish harboring infective larvae eaten by dogs or people.
L1 larvae consumed by a copepod.
5
2
Female worm begins to emerge from skin one year after infection.
3
Fertilized female worm migrates to surface of skin, causes a blister, and discharges larvae.
4
L1 larvae released into water from the emerging female worm.
CDC

FIGURE 8.17 Life cycle of *dracunculus medinensis*.

8.4.2 Platyhelminthes (flat worm)

- Do not have digestive tract
- Classified into
  - Trematodes (flukes-worm)
  - Cestodes (tapeworm)

8.4.2.1 Trematodes (Fig. 8.19)

- Leaf-like unsegmented body shape with incomplete alimentary canal, no anus
- Flatworm infects blood vessels, liver, lungs, and gastrointestinal tract
- Body is usually flat, with oral suckers, but no hooks
- Hermaphrodites → having both male and female organs

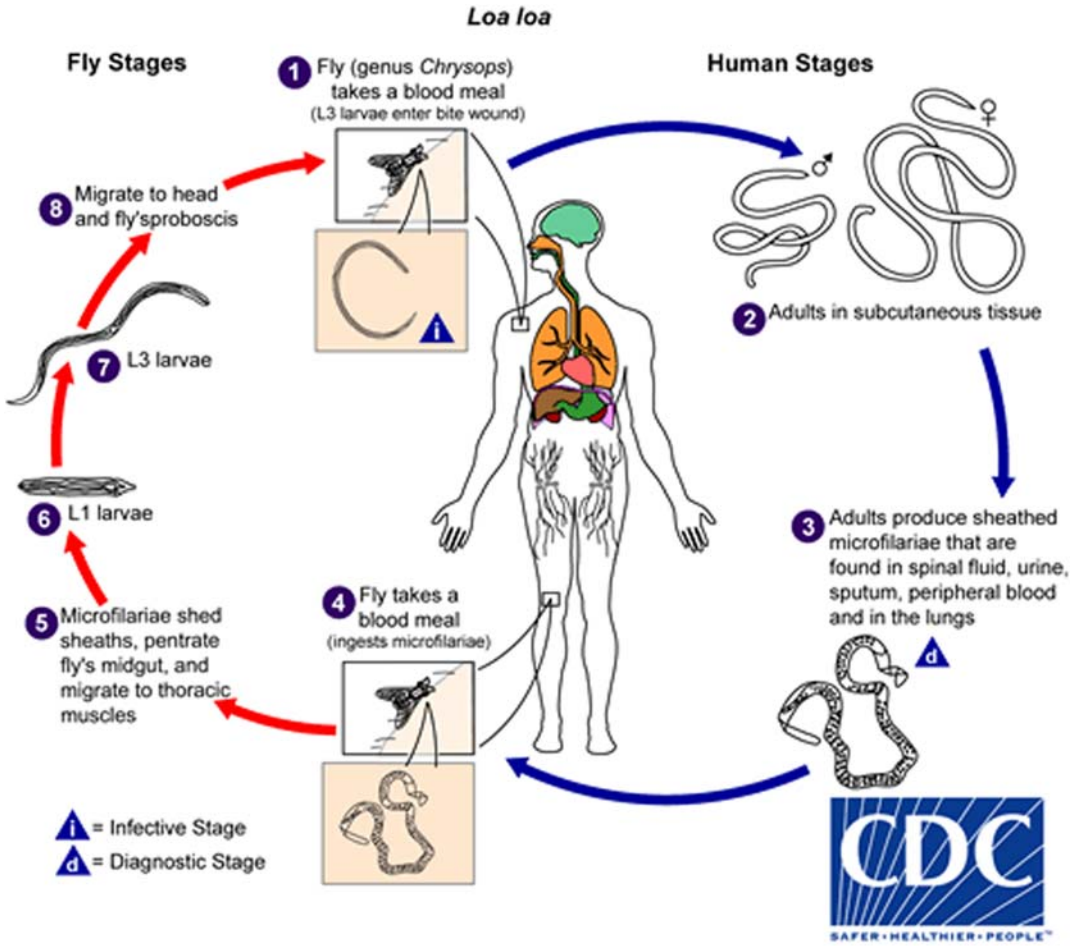
Loa loa
Fly Stages
Human Stages
1 Fly (genus Chrysops) takes a blood meal
(L3 larvae enter bite wound)
2 Adults in subcutaneous tissue
3 Adults produce sheathed microfilariae that are found in spinal fluid, urine, sputum, peripheral blood and in the lungs
4 Fly takes a blood meal
(ingests microfilariae)
5 Microfilariae shed sheaths, pentrate fly's midgut, and migrate to thoracic muscles
6 L1 larvae
7 L3 larvae
8 Migrate to head and fly'sproboscis
i = Infective Stage
d = Diagnostic Stage
CDC
SAFER·HEALTHIER·PEOPLE™

FIGURE 8.18 Life cycle of Loa loa.

- Includes:
  - Schistosoma species
  - Clonorchis sinensis
  - Paragonimus species

8.4.2.1.1 *Schistosoma* sp.

- Three major species
  - *Schistosoma japonicum* → Eastern Asia.
  - *Schistosoma mansoni* → South Africa and other parts of Africa.
  - *Schistosoma haematobium* → Africa.
- Transmission
  - Found in freshwater, penetrate the exposed skin, and migrate to the venous system where they mate and lays eggs
  - Snail is the intermediate host
- Infections
  - Swimmer's itch → Cercariae penetrate the skin and cause intense itching, papular or urticarial rash at the site of entry.

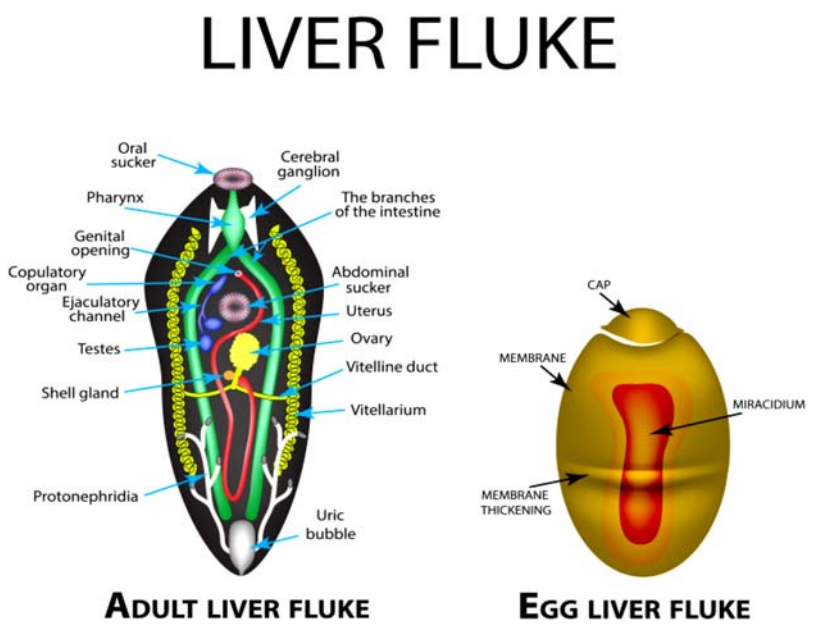

FIGURE 8.19 Liver fluke (trematode).

  - Katayama fever → Usually, after 1–4 weeks of infection, the patient develops fever, hives, headache, myalgia, cough, enlarged lymph nodes, liver, and spleen with eosinophilia. Flu-like symptoms.
  - Chronic infections → Eggs released by the organism that does not expel with feces or urine result in deposition in various organs. Immune systems wall them off and form granulomas
- Life cycle (Fig. 8.20):
- Sign and symptoms: based on where the organism or the eggs are deposited in the body.
  - GI symptoms: abdominal pain, diarrhea, hepatomegaly/fibrosis, portal hypertension, and GI bleeding
  - Pulmonary: dyspnea, cough, and pulmonary hypertension
  - CNS: headache, nystagmus, delirium, seizure, and focal neurological deficit
  - *S. haematobium* eggs are deposited in the bladder, resulting in hematuria, and dysuria. Prolong infection may result in ulceration and papillomatous mass which may lead to squamous cell carcinoma of the bladder
- Differential diagnosis:
  - Salmonellosis, hepatitis, Crohn disease, ulcerative colitis, and HIV
- Diagnosis
  - Microscopic exam of stool or urine for eggs
  - Biopsy of granulomas → egg filled granulomas
  - Antigen tests

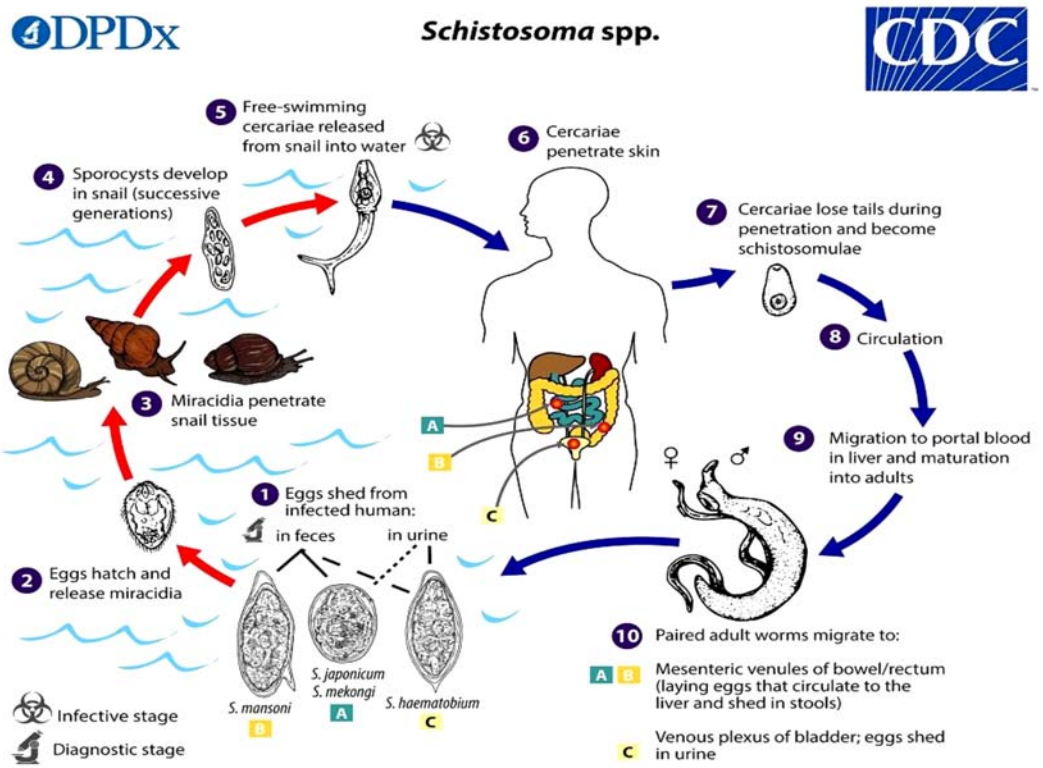
DPDx
Schistosoma spp.
CDC
5 Free-swimming cercariae released from snail into water
6 Cercariae penetrate skin
4 Sporocysts develop in snail (successive generations)
7 Cercariae lose tails during penetration and become schistosomulae
8 Circulation
3 Miracidia penetrate snail tissue
9 Migration to portal blood in liver and maturation into adults
1 Eggs shed from infected human:
in feces
in urine
2 Eggs hatch and release miracidia
10 Paired adult worms migrate to:
A B Mesenteric venules of bowel/rectum (laying eggs that circulate to the liver and shed in stools)
C Venous plexus of bladder; eggs shed in urine
S. mansoni
S. japonicum
S. mekongi
S. haematobium
Infective stage
Diagnostic stage

FIGURE 8.20 Life cycle of schistosoma species.

- Serology tests
- Chest X-rays, MRI, or CT scan → shows calcifications
- History of traveling in endemic areas and freshwater contact

- Treatment
  - Praziquantel (40 mg/kg po × 1–3 doses ± prednisone
  - Praziquantel does not kills eggs or schistosomula. Repeat the treatment again after 2–3 months

8.4.2.1.2 *Clonorchis sinensis* (Chinese fluke worm)

- Cause clonorchiasis
  - Infestation of common bile duct
- Transmission
  - Eating raw, undercooked freshwater fish or shrimp.
  - Inside human guts, metacercariae (resting or maturing stage larvae) are released in the duodenum. From duodenum they enter into common bile duct to intrahepatic, gallbladder or pancreatic ducts, where they mature into adult worms.
  - Snail is an intermediate host.

- Affected area
  - Eastern Asia.
- Life cycle (Fig. 8.21):
- Sign and symptoms
  - Mostly asymptomatic
  - Right upper quadrant pain, jaundice, diarrhea, weight loss, and eosinophilia
  - Complications
    - Cholangitis, cholelithiasis, pancreatitis, and cholangiocarcinoma
- Diagnosis
  - Microscopic examination of stool for eggs
  - X-ray → shows intrahepatic calcifications
  - Hepatic ultrasound, CT, or MRI
  - Serology
  - PCR
- Treatment
  - Praziquantel (25 mg/kg po tid × 2 days)
  - Albendazole (10 mg/kg po daily × 7 days)
  - Surgery

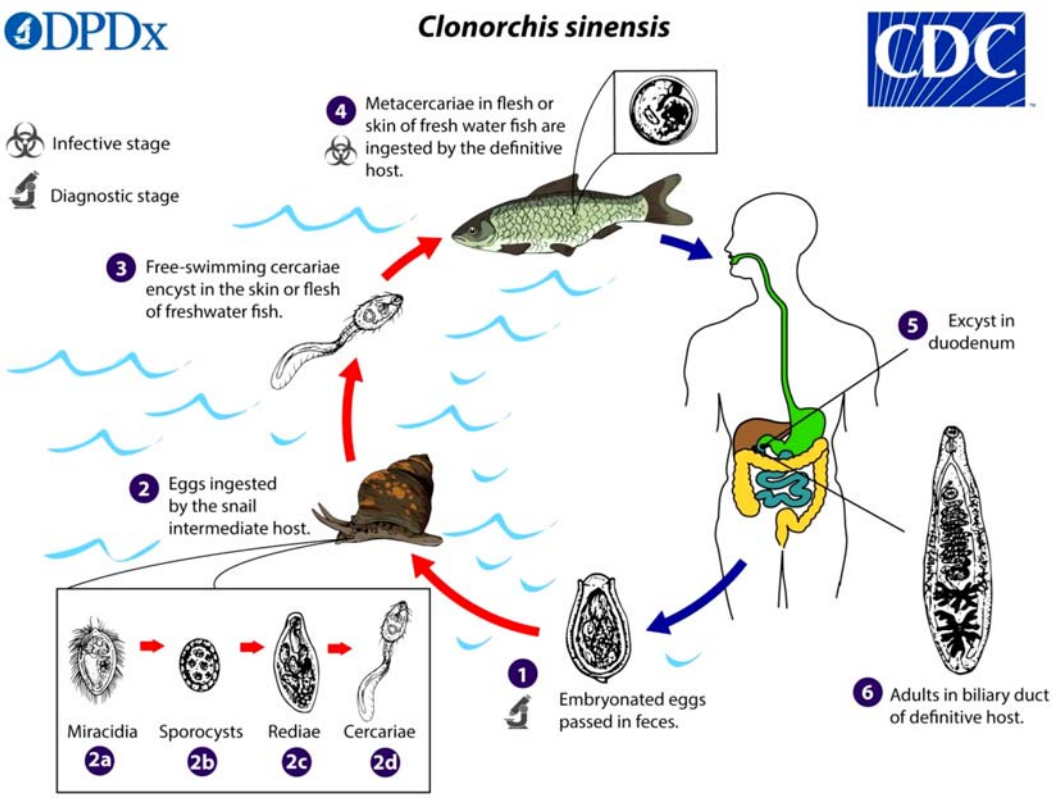

FIGURE 8.21 Life cycle of *Clonorchis sinensis*.

8.4.2.1.3 Paragonimus wetermani

- Lung flu infects the lungs
- Cause pulmonary paragonimiasis
- Transmission
  - Snail and crustaceans (crabs and crayfish) are the intermediate hosts.
  - Humans get infected by eating raw or undercooked crabs or crayfish.
  - Parasite penetrates the intestinal wall and reaches the lungs, encapsulated, and produce eggs.
  - Eggs exit the body via coughing up sputum or swallowed up and passed through feces.
  - Worm may reach to brain, liver, lymph nodes, and other tissue.
- Affected area
  - China, Japan, Philippines, and Vietnam
- Life cycle (Fig. 8.22):

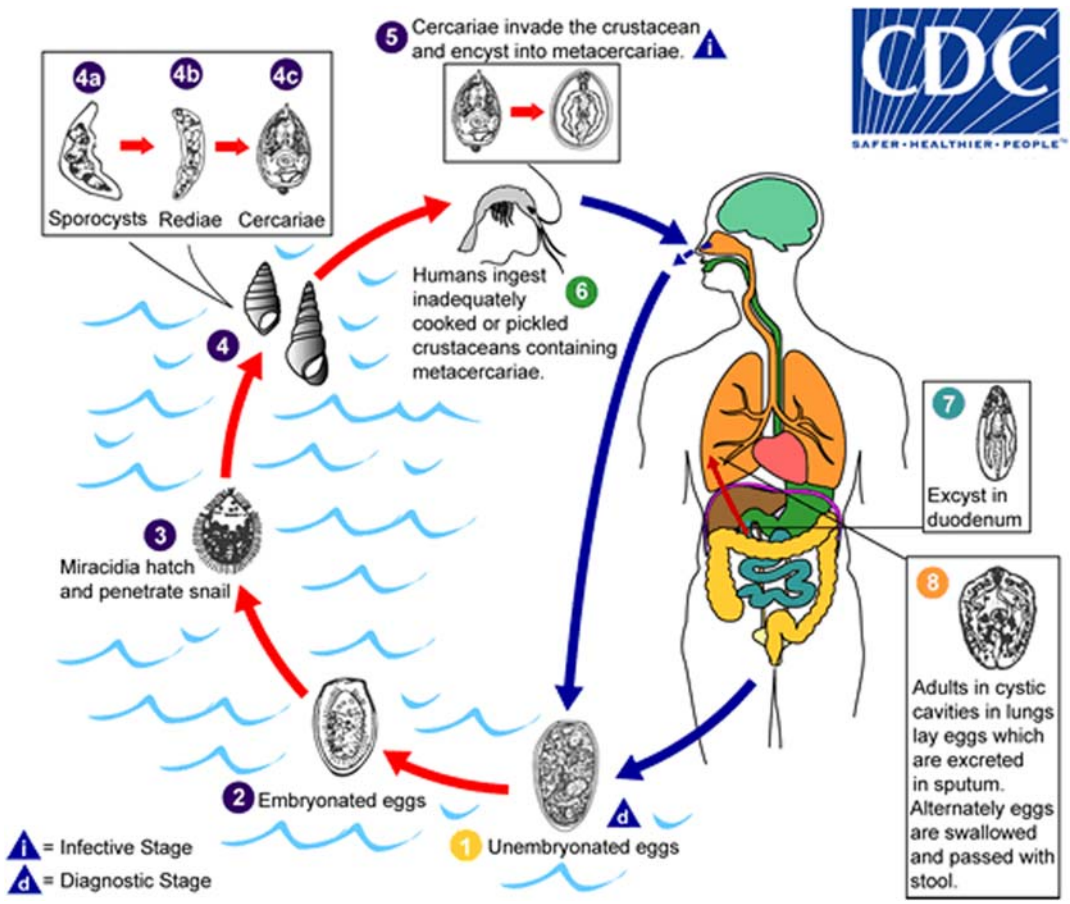

FIGURE 8.22 Life cycle of *Paragonimus watermani.*

- Sign and symptoms:
  - Fever, cough, dyspnea, chest pain, and hemoptysis
  - Chronic phase: Other organs are infested. Seizure, aphasia, paresis visual disturbance, meningitis, and encephalitis
  - Diagnosis
  - Microscopic exam of stool for eggs
  - Serology tests
  - X-rays and CT
  - Treatment
  - Praziquantel (25 mg/kg po TID × 2 days)
  - Triclabendazole (10 mg/kg po q12h × 2 doses)

8.4.2.2 Cestodes (tapeworm) (Table 8.2; Fig. 8.23)

- Tape-like segmented body shape with suckers and hooks. No alimentary canal, no body cavity, and hermaphrodite
- Three stages →veggs, larvae, and adults
- Adult worms live in the mammalian intestine, where it lays eggs that are excreted into feces and consumed by intermediate host (pigs, cows, fish, etc.). Eggs are hatched into larvae that enter the circulation and form a cyst in muscles and other organs.
- When the intermediate host is eaten raw or undercooked, encyst larvae develop into adult worms in the gut of a definite host.
- Worms are named after the intermediate host.
- Diagnosis
  - All cestodes are diagnosed by microscopic exam of stools for eggs
  - X-rays, CT, or MRI −> larvae
  - Serological tests
- Treatment
  - Praziquantel
  - Albendazole

Table 8.2 Cestodes.

Common name	Family	Clinical sign	Remarks
Fish tapeworm	*Diphyllobothrium latum*	Abdominal discomfort, diarrhea, and weight loss. Vitamin B12 deficiency	Largest worm
Beef tapeworm	*Taenia saginata*	Mild gastrointestinal symptoms	
Pork tapeworm	*Taenia solium*	Mild gastrointestinal symptoms Blindness Seizure, focal neurological deficit Hydrocephalus	Larvae (cysticerci) can invade eyes and brain

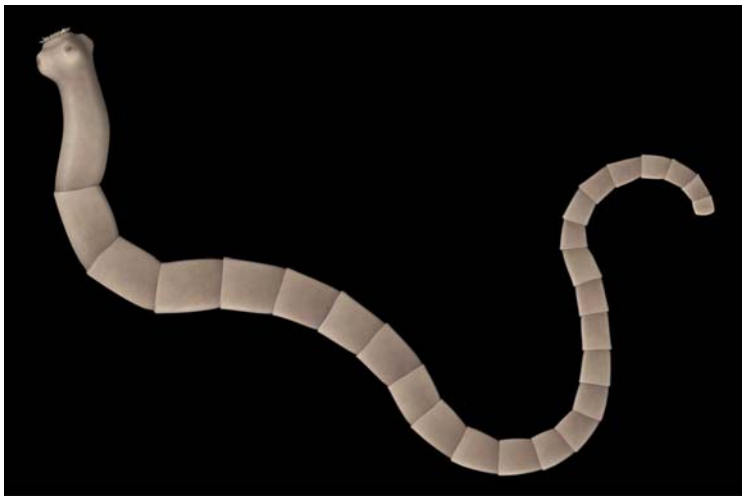

FIGURE 8.23 Cestodes (tapeworm).

8.4.2.2.1 *Echinococcus granulosus or E. multilocularis*

- Differ from the rest of the group as dogs are the definite host
- Human and herbivores are the intermediate hosts
- Eggs are ingested while handling infected dogs or eating or drinking contaminated food, water, or soil
- The larvae form hydatid cyst in liver (*E. granulosus*) and lungs (*Echinococcus multilocularis*)

- Sign and symptoms:
  - Liver cyst: upper abdominal pain, jaundice, and poor appetite
  - Lung cyst: cough, chest pain, dyspnea, and hemoptysis
- Diagnosis
  - CT or ultrasound → cyst in liver or lungs
  - Serology
- Treatment:
  - Albendazole or metronidazole
  - Surgery or percutaneous aspiration

8.5 Antiparasitic drugs (Tables 8.3, 8.4)

Table 8.3 Antiparasitic drugs.

Drug	Indication	Adult dosage	Side effects
Atovaquone	Babesiose PCP (prevention) PCP (treatment) Toxoplasmosis	750 mg bid 1500 mg daily 750 mg bid × 21 days 1500 mg daily	Rash, nausea, vomiting, abdominal pain, headache, fever, insomnia, and anemia
Eflornithine	*T. b. gambiense*	400 mg/kg/day, divided inti q12h × 7—10 days. Use in combination with other drugs	Diarrhea, vomiting, abdominal pain, bone marrow suppression, thrombocytopenia, leukopenia, and seizure
Melarsoprol	Trypanosomiasis with CNS involvement, *T. b. rhodesiense*	2.2 mg/kg/day IV × 10 days	Encephalopathy, nausea, vomiting, and abdominal pain. 50% mortality rate. Do not use it if g-6-phos deficiency
Nifurtimox	Chagas disease, combination with eflornithine for W. African trypanosomiasis	8—10 mg/kg/day, divided into 4x/day for 90—120 days 15 mg/kg/day divided into q8h × 10 days with eflornithine	Abd pain, N/V, diarrhea, wt loss, irritability, restlessness, anxiety, peripheral neuropathy, and ↑liver enzymes
Nitazoxanide	Cryptosporidium, giardia	500 mg po bid × 3 days with food	Abd pain, diarrhea, discolored eye andand urine
Pentamidine	W. African trypanosomiasis. Second-line treatment for *P. jiroveci*	4 mg/kg daily × 7—10 days (IV or IM)	Electrolytes abnormality, thrombocytopenia, nephrotoxicity, and pancreatitis
Stibogluconate	Leishmaniasis	20 mg/kg/day IV/IM × 20 days 20 mg/kg intra-lesion for mild disease	Weakness, malaise, headache, ↑liver enzymes, cytopenia, pprolongation of QTc wave
Suramin	*T. rhodesiense* (CNS involvement)	1 gm IV on days 1, 3, 7, 14, 21	Nephrotoxicity, hepatotoxicity, rash (exfoliative), agranulocytosis, and anemia

Table 8.4 Antimalarial drugs.

Drug	Indication	Adult dose	Side effects
Antimalarial drugs			
Artemether-Lumefantrine	All malaria sp *P. falciparum* (US)	4 tablets q8h × 2 doses, then 4 tablets q12h × 2 days	Headache, anorexia, dizziness, myalgia, and QT prolongation
Artesunate	Severe malaria, all malarial sp.	2.4 mg/kg iv @ 0, 12, 24 h	Postartesunate delayed hemolysis
Chloroquine	Nonresistance *P. falciparum, P. malariae, P. ovale, and P. knowlesi*	500 mg q week, starting 1—2 wks prior to departure, continue while in the area and 4 weeks after return (prophylaxis). Use in combination with primaquine for the *P. vivax* and *P. ovale*	Color vision change, retinal damage, GI problems, and hemolytic anemia in patients with G6PD deficiency

Continued

Table 8.4 Antimalarial drugs.—cont'd

Drug	Indication	Adult dose	Side effects
Mefloquine	*P. falciparum* Not a first choice	250 mg once a week (prophylaxis) 750-120 mg × 1 then 500 mg q8h	Black box warning for neuropsychiatric and vestibular problems
Primaquine	Liver stage of *P. vivax,* *P. ovale,* and *P. falciparum*	30 mg (base) daily × 14 days (treatment) 30 mg (base) daily, start 1 day before exposure and continue 7 days after return. (prophylaxis)	Hemolytic anemia in G6PD-deficient patients
Atovaquone-Proguanil	Malaria (prevention) Malaria (treatment)	1 tab daily, start 1—2 days prior to departure continue during the stay and 7 days after return 1 gm—400 mg po daily × 3 days	Rash, GI disturbance, headache, N/V, and ↑ALT/AST
Pyrimethamine-Sulfadoxine	Chloroquine-resistance *P. falciparum*	Use for intermittent prophylaxis treatment of malaria in pregnant women	Folate deficiency, ↓WBC and platelets, photosensitivity, rash, and diarrhea

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9 Common infections caused by multiple microorganisms

9.1 Respiratory infection

a) Upper respiratory infection;
b) Lower respiratory infection

9.1.1 Upper respiratory infection

9.1.1.1 Pharyngitis/tonsilitis (see Fig. 9.1)

- Infection of the pharynx, which can be viral, bacterial, or noninfectious (Table 9.1).
- Infection is more common in children ages 3–14 years old.
- Viruses are the common cause of pharyngitis. Viruses that cause pharyngitis include: Influenza virus, parainfluenza virus, EBV, CMV, and COVID-19.
- Bacterial pharyngitis is commonly caused by Group A Streptococcus (GABHS = Group A Beta-Hemolytic Streptococcus).
- Uncommon bacterial cause of pharyngitis includes gonorrhea, diphtheria, mycoplasma, and chlamydia.
- Signs and symptoms:
  - Viral pharyngitis/tonsilitis:
    - Low grade fever, sore throat, voice hoarseness, nasal congestion, cough, ± conjunctivitis, erythema and edema of pharynx or tonsils, no exudates, and nontender cervical lymphadenopathy.
  - Bacterial pharyngitis/tonsilitis: Also see Section 2.2.2
    - Sore throat, tonsillar exudate, palatal petechia, tender cervical adenitis, and high-grade fever. Cough and rhinorrhea are mostly absent.
- Diagnosis
  - Clinical criteria, each symptom has one point (Strep throat)
    - Tonsillar exudate
    - Tender cervical adenitis
    - Fever
    - Absent of cough
    - Ages 3–14 = 1 point, ages 14–45 = no points, age >45 = −1 point.
    - Patients with 0–1 points unlikely have GABHS.
    - Patients with 2–3 points likely have GABHS

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  - Patient with four or more has a high chance of GABHS
  - Rapid antigen detection test (RADT): sensitivity is 77%–90%. Specificity is 88%–99% in adults.
  - Throat culture: 90%–95% sensitive and have a specificity of 95%–99%.
  - DNA probe
- Treatment:
  - Viral: Supportive
  - Bacterial:
    - Penicillin, amoxicillin, first or second generation cephalosporin,
    - macrolide, Clindamycin, Amoxicillin-clavulanate.
    - Ceftriaxone + Azithromycin if gonococcal.
      Note: do not use antibiotics if suspected of EBV.
      Aspiration or drainage in case of abscess
- Poststrep Complications → Delayed antibody mediated → Please see Section 2.2.2
  - Rheumatic fever———reversible
  - Glomerulonephritis————not reversible

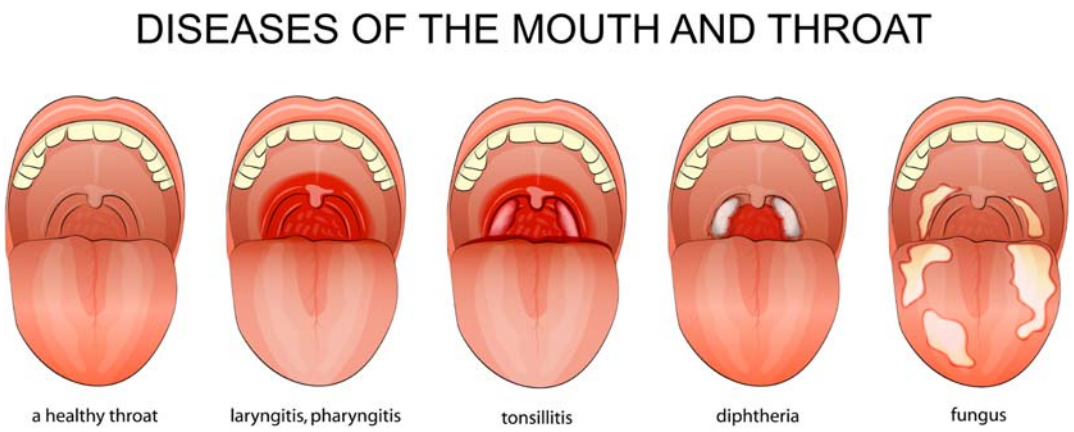

FIGURE 9.1 Diseases of the mouth and throat.

Table 9.1 Difference between viral and bacterial pharyngitis.

Symptoms	Viral pharyngitis	Bacterial pharyngitis (GABHS)
Cough and runny nose	Common	Uncommon
Fever	Low grade	>38°C
Ages	Any age	Children, adult >45 highly unlikely
Pharynx/tonsil	Erythematous	Erythematous/exudate
Adenopathy	±Tender	Tender
Odynophagia	Mild	Severe

Note: Pt age >45 highly unlikely has GABHS pharyngitis.

9.1.1.2 Peritonsillar and retropharyngeal abscess

- Peritonsillar abscess develop around palatine tonsils and usually infect adults, while retropharyngeal abscess developed behind the pharynx and usually infect toddlers and young children
- Etiology:
  - Streptococcus and Staphylococcus sp.
  - Bacteroides (anerobic)
- Signs and symptoms:
  - Fever, unilateral sore throat, dysphagia, cervical adenopathy at the site of abscess, voice change, drooling, tonsillar erythema, and exudate.
- Diagnosis:
  - Needle aspiration and culture
  - CT of the neck
- Treatment:
  - Drainage
  - Antibiotics
    - High dose IV penicillin, amoxicillin-clavulanate, first-generation cephalosporin
    - Clindamycin, Metronidazole IV + IV ceftriaxone

9.1.1.3 Epiglottitis

- Life-threatening rapidly progressive.
- Inflammation and swelling of epiglottis and surrounding structure result in the obstruction of the upper respiratory tract.
- Bacterial infection is the most common cause, but viral and noninfectious causes are also possible
- Causative organisms are
  - S. *pneumoniae*
  - *S. aureus*
  - *H. influenzae* → elderly, immunocompromised, and unvaccinated patients.
  - Beta-hemolytic streptococci.
- Sign and symptoms:
  - Fever, sore throat, odynophagia, dysphagia with drooling.
  - Cough, inspiratory strider, dyspnea, dysphonia, and toxic appearance.
- Diagnosis:
  - Clinical (in the case of respiratory distress, secure the airway).
  - Direct observation only in the operating room with advanced airway intervention (Examination may progress to complete obstruction).
  - Lateral neck X-ray → thumb sign (enlarged epiglottis).
- Differential diagnosis (Table 9.2)
  - Croup → see Section 6.3
  - Foreign body aspiration → Visible in X-ray
  - Bacterial tracheitis
  - Retropharyngeal abscess

www.images.google.com.
"epiglottitis" see thumb sign on lateral X-ray.

- Treatment
  - Secure airways
  - Ceftriaxone (50–75 mg/kg q24h) + Vancomycin 15–20 mg/kg
  - Levofloxacin 100 mg/kg q24h + Clindamycin 7.5 mg/kg q6h
  - Dexamethasone IV
  - Nebulized with racemic epinephrine
- Prevention
  - Hib vaccine

Table 9.2 Difference between epiglottis and croup.

	Epiglottitis	Croup
Causes	Mostly bacterial	Viral
Ages	2–8 years	6 months–3 or 4 years
Onset	Abrupt	Gradual
Barking cough	Uncommon	Common
Drooling and dysphagia	Common	Uncommon
X-ray	Thumb sign (Enlarged epiglottis)	Steeple sign (Normal size epiglottis)

9.1.1.4 Common cold

- Commonly caused by Rhinovirus (30%–50%), Coronavirus (10%–15%), RSV, and Parainfluenza virus (5%–6%)
- Signs and Symptoms: Runny and congested nose with clear discharged, fever usually low grade, scratchy throat, cough, sneezing, headache, malaise, myalgia
- Risk factors:
  - Daycare
  - Smoke exposure
  - Diagnosis: clinical
  - Differential diagnosis:
  - Influenza
  - Sinusitis
  - Pharyngitis
- Treatment: symptomatic treatment, rest, humidifier, Acetaminophen, and other OTC

9.1.1.5 Influenza: also see the viral Section 6.3.1

- Caused by influenza virus A or B.
- Endemic in fall and winter season.
- Highly contagious and infect any age group, but children and the elderly are more susceptible.
- Sign and Symptoms (Table 9.3):
  - Runny and congested nose, body ache, headache, fever, nroductive cough, malaise, tearing or burning eyes
- Diagnosis:
  - clinical, rapid antigen test (high specificity with low sensitivity). RT-PCR
- Treatment:
  - Symptomatic, rest, ↑fluid intake, humidifier, Acetaminophen, and other OTC.
  - May use Oseltamivir 75 mg (oral) at the first sign of flu
  - Zanamivir is a nasal inhaler
- Complication: Pneumonia and secondary bacterial infection
- Prevention: Flu vaccine.
- Antigenic Drift:
  - Influenza virus has two antigens on the surface, hemagglutinin (H), and glycoprotein neuraminidase (NA). Slight change in these antigens results in new strains called antigen drift. Every year these changes result in the modification of vaccine.
- Antigenic Shift:
  - New combination of H and NA antigens result in the new viral genome and is called antigenic shift, such as virus associated with SARS, Vivian influenza, swine flu, and Spanish flu.

Table 9.3 Difference between cold and flu.

Symptoms	Cold	Flu
Fever	Low grade to none	Yes
Body aches/chills	Not common	Common
Sneezing	Common	Not common
Fatigue/weakness	Not common	Common
Cough	Mild to none	Moderate
Stuffy nose/sore throat	Common	Common
Headache	Yes/No	Yes

9.1.1.6 Sinusitis

- Inflammation of nasal and paranasal cavity.
- Further classified into:
  - **I.** Acute <4 weeks,
  - **II.** Subacute = 4−12 weeks

III. Chronic >12 weeks
IV. Recurrent = 4 episode/year

- Most cases are viral, especially in children.
- Rhinovirus, influenza virus, and parainfluenza virus are the most common viruses involved.
- Bacterial sinusitis is caused by *Streptococcus pneumoniae*, *H. influenza*, Catarrhalis, and Staphylococcus.
- Hospital acquired sinusitis may involve *S. aureus, K. pneumonia and P. aeruginosa.*
- Fungal sinusitis involves Aspergillus or Mucor
- Sign and Symptoms:
  - Nasal discharged and congestion
  - Sinus pressure
  - Headache
  - Fever and malaise
- Diagnosis: clinical, CT scan. CT should be avoided in children
- Difference between viral and bacterial sinusitis
  - **Consider bacterial sinusitis if any of the following symptoms present**
    - Symptoms last longer than 10 days
    - Worsening of the symptoms
    - Severe symptoms with fever >32°C (102° F)
    - Purulent nasal discharge or maxillary tooth pain
- Treatment:
  - Amoxicillin-clavulanate, Amoxicillin.
  - Doxycycline, Clindamycin +third-generation cephalexin, Levofloxacin.
  - For fungal sinusitis, use Voriconazole, Itraconazole.

9.1.2 Lower respiratory tracks infection

9.1.2.1 Bronchitis: (acute)

- Inflammation of bronchi and the lining of bronchial tubes (Figs. 9.2 and 9.3)
- Usually viral 95% →Rhinovirus, parainfluenza, influenza A&B, RSV, Coronavirus.
- Bacterial cause→ *M. pneumoniae, B. pertussis*, Chlamydia,
- Chronic bronchitis is associated with smoking and other pollutants
- Sign and Symptoms:
  - Productive cough, ± fever, dyspnea, wheezing, rhonchi
- Diagnosis:
  - Clinical, chest X-ray to rule out pneumonia, nasopharyngeal swab for influenza and pertussis
- Differential diagnosis
  - Pneumonia
  - Influenza or cold
  - Sinusitis

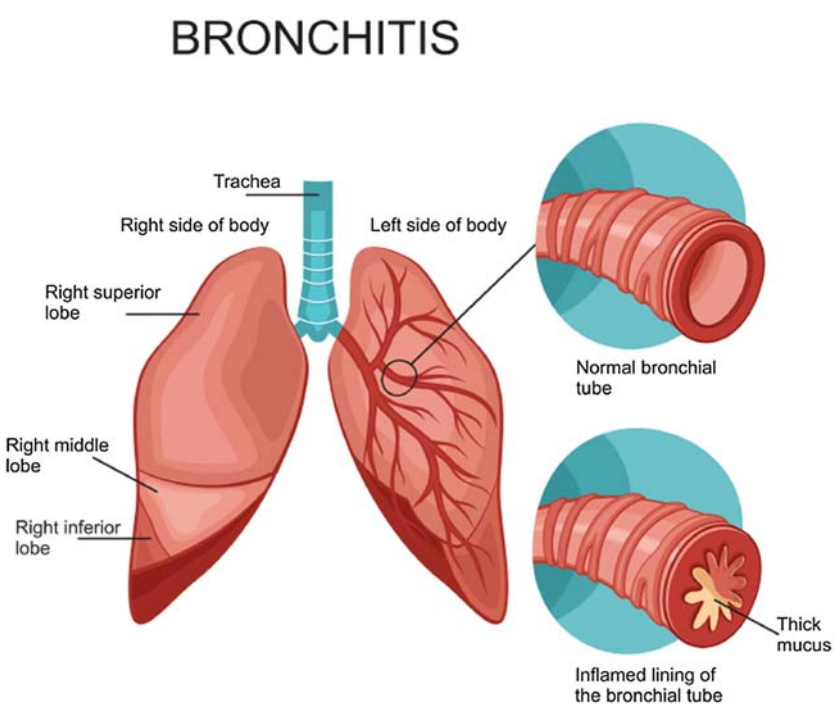

FIGURE 9.2 Bronchitis.

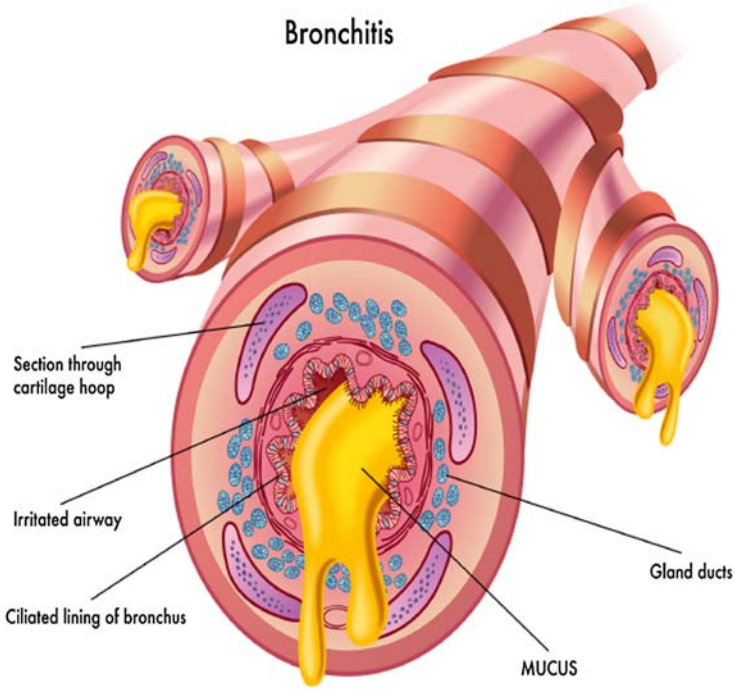

FIGURE 9.3 Bronchitis (inflammation and thick mucus in bronchial tube).

  - Tuberculosis
- Treatment:
  - Acetaminophen, inhaler, antitussive, hydration.
  - Antibiotics if it is bacterial.
    - Azithromycin, or clarithromycin.
    - TMP-SMX

www.images.google.com “bronchitis”

9.1.2.2 Bronchiolitis

- Inflammation of the bronchioles (medium and small branches)
- Edema and exude result in obstruction and air trapping
- Usually, affect very young children and occurs in epidemics
- Mostly caused by viruses, such as RSV, Rhinovirus, parainfluenza
- Sign and symptoms:
  - Cough, fever, wheezing, crackle, tachypnea, and respiratory distress syndrome
  - Hospitalization may be required.
- Diagnosis: history, epidemic, rapid assay for RSV antigen on nasal washing or nasal aspiration, chest X-ray
- Differential
  - Pneumonia
  - Asthma
  - Foreign body aspiration
  - Bronchopulmonary dysplasia
- Treatment: supportive, O2, and IV hydration.

9.1.2.3 Pneumonia

- Inflammation of the lung parenchyma with impairs gas exchange.
- Caused by: viruses, bacteria, protozoa, fungus, and mycobacteria.
- Classified into:
  - Lobular pneumonia. Consolidation in one lobe.
  - Bronchopneumonia: Scattered consolidation.
- Also classified into
  I. Community Acquired Pneumonia (CAP):
  II. Hospital Acquired Pneumonia (HAP) which also includes Ventilator acquired
  III. Aspiration pneumonia

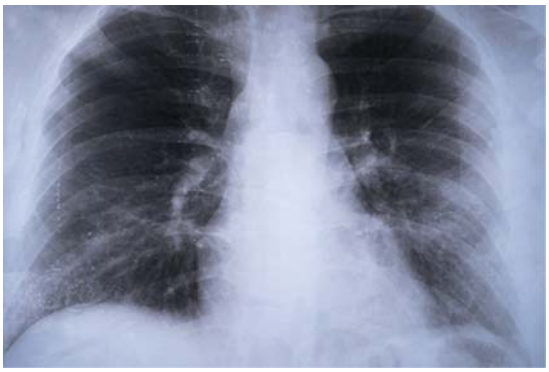

FIGURE 9.4 Viral pneumonia.

- Bacterial causes of pneumonia → *S. pneumoniae, M. catarrhalis, H. influenzae, S. aureus*, GAS (group A streptococcus) (Fig. 9.5).

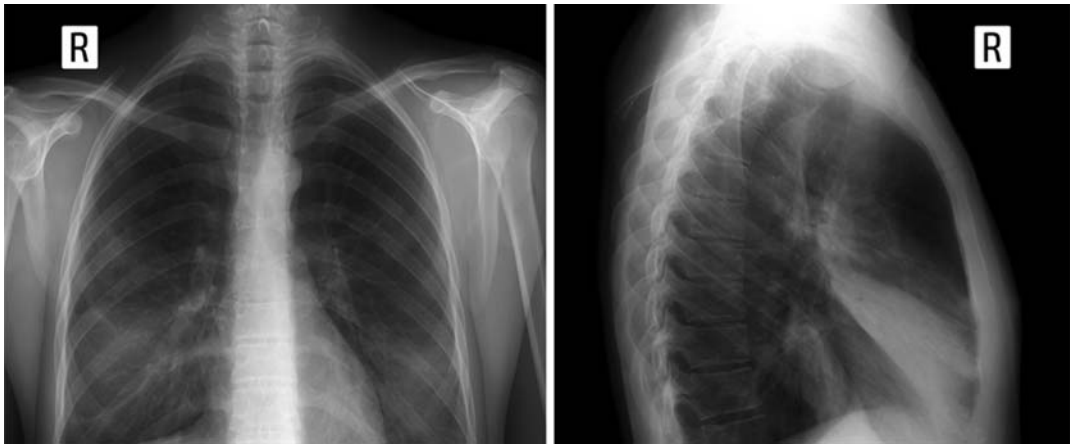

FIGURE 9.5 Bacterial pneumonia.

- Atypical pneumonia caused by → *C. pneumoniae*, *M. pneumoniae* and Legionella.
- Viral causes of pneumonia → RSV, adenovirus, influenza virus, and SARS-2 CoV (Fig. 9.4)
- Cystic fibrosis, AIDs and neutropenic, bronchiectasis → *P. aeruginosa.*
- Fungus pneumonia, immune compromise patient→ histoplasma, *Coccidioides immitis*
- Sign and Symptoms:
  - Fever, cough, fatigue, dyspnea, chills.
  - Crackles, bronchial breath sound and egophony on auscultation
- Criteria for hospitalization:
  - These criteria are used as a guide to decide if to admit a patient in a hospital

- CURB-65 is the most commonly used criteria as PSI is complicated and is not easy to use. It required laboratory values (Table 9.4).
- Each criterion has one point, and points above or equal to two consider hospitalization.
  Points 0–1 ———————— out patient
  Points two ————Hospitalization
  Points 3 or more————————ICU

Table 9.4 PSI versus CURB-65.

Pneumonia severity index (PSI)	CURB-65
Hypotension SPB < 90, DBP < 60 mmHg	Confusion
Respiratory rate > 30/min	Uremia (BUN >19 mg/dL
Mechanical ventilation is required	Respiratory rate > 30 b/min
$PaO_2/FiO_2 < 250$	BP systolic < 90 or DBP < 60
Confusion	Age ≥ 65
BUN > 19.6 mg dL	
Multilobar pneumonia	

- Diagnosis (Table 9.6)
  - Clinical
  - Chest X-ray
    - Multi-lobar infiltrate → *S. pneumonia*, Legionellae.
    - Interstitial infiltrate → Viral, *M. pneumonia.*
    - Cavitating infiltrate → *S. aureus* or fungal.
      ➢ It is usually not possible to differentiate one type of pneumonia from other types by looking at the chest X-ray.
    - Sputum: gram stain, PCR, culture
    - Urine antigen testing: Legionella and Pneumococcal antigen.
    - Elisa or PCR for HSV. Influenza A and B, and Cytomegalovirus.
    - Serum antigen testing for Cryptococcus and Aspergillus.
    - Beta-D-glucan testing for fungal pathogen.
- Differential
  - Heart failure
  - COPD (acute)
  - Influenza
  - Bronchitis (acute)
- Klebsiella pneumonia causes red jelly like sputum.
- Treatment: see the chart below (Table 9.5).

Table 9.5 Type of pneumonia and treatment.

Type of pneumonia	Most common bacteria	Treatment
Community acquired pneumonia (CAP). Outpatient treatment.	*S. pneumonia*, *M. catarrhalis*, *H. influenza*, *S. aureus*, GAS. Atypical bacteria: *M. pneumonia*, *C. pneumoniae*, Legionella	a) No modified[1] factors: macrolide or doxycycline b) With modified[1] factors: respiratory fluroquinolone or beta-lactum[2] + macrolide
Community acquired pneumonia. Inpatient (ward) treatment	Same as above	Respiratory fluoroquinolone or beta-lactam[2] + macrolide
CAP ICU	Same as above	Beta-lactam + macrolide or respiratory fluoroquinolone
Hospital acquired pneumonia/ventilator associated pneumonia,	*P. aeruginosa*, *S. aureus* including MRSA, enteric GNB	No risk factors[3] = ceftriaxone + respiratory fluoroquinolone. With risk factors and late onset >5 days, antipseudomonal antibiotics such as, piperacillin/tazobactam, cefepime, levofloxacin, carbapenem + anti-MRSA Vancomycin or linezolid
Aspiration pneumonia	Oral anaerobes, enteric gram negative bacteria, *S. aureus*, Streptococcus	Levofloxacin + metronidazole, clindamycin ± levofloxacin or ampicillin/sulbactam For nosocomial: Piperacillin/tazobactam. Carbapenem ± clindamycin or metronidazole
Pneumonia in immunocompromised	*P. jiroveci*, fungi, Nocardia, CMV, HSV. Plus, common bacterial pathogens such as *S. pneumonia*.	TMP-SMX, dapsone/TMP, clindamycin/primaquine, broad spectrum antibiotics such as use in HAP/VAP. CMV → ganciclovir or valganciclovir. HSV → acyclovir Fungus → voriconazole, fluconazole, or amphotericin B
Alcoholic	Klebsiella, enteric, GNB, *S. aureus*, anaerobe	Same as aspiration pneumonia

[1]Modified, use of antibiotic in last 3 month,
[2]Beta-lactam = cefotaxime, ceftriaxone, ampicillin/sulbactam
[3]Risk factors = multidrug resistance.

Table 9.6 Difference between viral and bacterial pneumonia.

Viral pneumonia	Bacterial pneumonia
Usual initial symptoms are congestions,	Initial symptoms are more severe with high
Cough and mild to moderate fever	Fever, chest pain, purulent sputum, tachypnea
Breath sound are unclear on both lungs	Breath sounds are normal on one side while absent on other
Chest X-ray shows diffuse involvement of lungs	Chest X-ray shows consolidation on one area

Note: This difference is not absolute, and there is always some cross over characteristics. Culture is the gold standard for the diagnosis.

9.2 Meningitis

- Inflammation of meninges and subarachnoid space.

9.2.1 Classification

- Bacterial meningitis
- Viral meningitis
- Noninfectious meningitis
- Fungal meningitis
- TB meningitis

9.2.2 Bacterial meningitis

- Classified into:
  - Community acquired: commonly caused by *S. pneumonia, N. meningitidis, H. influenza, Listeria*
  - Hospital acquired: Bacteria responsible are: *S. aureus*, Coagulase negative staph, *P. aeruginosa*, and other gram-negative bacilli.
- Sign and symptoms:
  - Malaise
  - Fever
  - Headache
  - Photosensitivity
  - Stiffness of the neck (Nuchal rigidity) may not be present in all patients.
  - Seizure, especially in children
  - Positive Brudzinski and Kernig's sign. Low sensitivity and high specificity.
    - Brudzinski sign: flexing the neck causes hips and knees to flex.
    - Kernig's sign: flexing the knee beyond 135 degrees cause back pain.
- Diagnosis:
  - Clinical signs and symptoms
  - CSF analysis (Table 9.7)
  - Blood culture and PCR

Table 9.7 CSF fluid in meningitis.

Condition	Protein	Cell type	Glucose	Test
Normal	<40 mg/dL	Lymphocytes 1–5 cells/uL	50–100 mg/dL	
Bacterial	Increased	Leukocytes, PMN increased	Low	Gm stain, culture, PCR
Viral	Increased	Increased lymphocytes	Normal	PCR. IgM
TB	Increased	Pleocytosis, mix PMN and lymphocytes	Low	Acid fast staining, PCR, culture, interferon-gamma
Fungal	Increased	Lymphocytes	Low	India ink staining, antigen test, culture

- CBC with differential
- Metabolic panel

Spinal Tap is contraindicated in high intracranial pressure, papilledema, focal neurologic deficits, seizure, immune compromise, and history of CNS disease, do CT or MRI before spinal Tap to check ICP.

N-meningitidis cause rash and petechiae on trunks.

Antibiotics (bactericidal) and corticosteroids should be started immediately if Pneumococcal meningitis suspected just after blood sample drawn.

- Treatment:
  - Age < 6week: Cefotaxime + ampicillin or ampicillin + Gentamicin. Add vancomycin if *S. pneumoniae*
  - Age 6wks-3 month: ampicillin + cefotaxime + vancomycin
  - Age >3 month and adults: Ceftriaxone + vancomycin. Add ampicillin if Listeria suspected. (community acquired)
  - Hospital acquired: Vancomycin + Cefepime, or Ceftazidime, or Meropenem
  - Add Dexamethasone 30 min before or with first dose of antibiotics for bacterial meningitis
  - Allergy to Penicillin (severe) → Vancomycin + Aztreonam or Ciprofloxacin or Moxifloxacin or TMP-SMX
- Prevention:
  - Vaccine against *H. influenza, S. pneumoniae, and N. meningitides*

9.2.3 Viral meningitis

- Most commonly caused by: HSV 1−2, VZV, Enteroviruses, West Nile virus, Parechoviruses
- Sign and symptoms are less severe than bacterial meningitis
- Treatment is usually supportive except if it is caused by HSV then Acyclovir is used for treatment.

9.2.4 Fungal meningitis

- Caused by Cryptococcus neoformans, var neoformans (type D strain)
- Coccidioides, Histoplasma, Blastomyces, Sporothrix, and Candida species are also associated with fungal meningitis.
- Coccidioides species are predominant in Southwest, Histoplasma, and Blastomyces in central and eastern U.S. region.
- Epidural methyl prednisone injections have been associated with fungal meningitis by species Exophiala dermatitidis and Exserohilum rostratum.
- Signs and symptoms are less severe than bacterial meningitis and usually acquire chronic form.
- Diagnosis:
  - cryptococcal antigen test, culture, and CSF analysis.
- Treatment
  - Amphotericin B + 5- fluorocytosine.
  - Patients with AIDs Amphotericin B + flucytosine followed by fluconazole.

9.2.5 Tuberculosis meningitis: also see Section 4.6

- Caused by *M. tuberculosis*
- Usually acquire chronic form
- May result in hydrocephalus, vasculitis with arterial or venous occlusion, cranial nerve II, VII, and VIII deficit.
- Diagnosis
  - Limited results
  - CSF analysis
  - Acid fast stain (only 30% sensitive)
  - Culture (70% sensitive also take up to 6 weeks to get the results)
  - PCR (50%–70% sensitive)
  - XPERT MTB/RIF → Nucleic acid amplification test use to detect *Mycobacterium tuberculosis* and resistance to rifampin (RIF) in less than 2 h.
- Treatment
  - Rifampin + isoniazid + pyrazinamide + ethambutol × 2 months followed by rifampin and isoniazid × 6–7 months.
  - Corticosteroid may be added if patient experienced neurological deficit.

9.2.6 Lyme disease meningitis: also see Section 4.5.2

- Caused by *Borrelia burgdorferi*, *B. afzelii*, and *B. garinii*
- Could be acute or chronic meningitis, usually developed slowly
- Diagnosis
  - History (spending time in a wooded area or traveling in endemic area)
  - Erythema migrans (characteristic for Lyme disease).

  - Facial palsy
  - CSF analysis
  - Serological test (ELISA) followed by Western blot
- Treatment:
  - Ceftriaxone (2 gm q24h) or cefotaxime (2 gm q8h) in hospitalized patients
  - Doxycycline (100 mg po bid) in ambulatory patient.
  - Second choice: Penicillin G

9.2.7 Syphilis meningitis: also see Section 4.5.1

- May be acute or chronic
- May cause cerebrovascular arteritis such as retinitis, seventh cranial nerve palsy.
- Diagnosis
  - CSF analysis
  - CSF and serum serological test followed by FTA-ABS
- Treatment
  - Penicillin G IV (3–4 million units) q4h × 10–14 days.
  - Ceftriaxone 2 gm q 24h × 14 days (not as effective as Penicillin).

9.3 Encephalitis

- Inflammation of the brain parenchyma
- Most common cause of encephalitis is viral infection caused by HSV, VZV, EBV, CMV, enteroviruses, West Nile virus, HIV, JC virus, rabies, polio and measles viruses.
- Other causes:
  - Bacterial: M. pneumonia, L. monocytogenes, spirochetes
  - Parasites: Toxoplasma
  - Fungus: Cryptococcus
  - Hypersensitivity postinfection: acute disseminated encephalomyelitis
  - Auto-antibody: Malignancy, anti-NMDA receptor
- Sign and Symptoms:
  - Fever, Headache, altered mental status, ± seizure, and neurological deficit, status epilepticus, coma, and death
  - Symptoms of viral encephalitis are less severe than bacterial encephalitis
- Diagnosis:
- MRI
  - CSF → analysis and culture
  - CT or MRI → characteristic temporal lobe involvement in HSV virus:
  - PCR
  - Culture
  - Serology

  - Brain biopsy
- Treatment:
  - Bacterial encephalitis → same as bacterial meningitis
  - Viral encephalitis → supportive, Acyclovir for HSV
  - Ganciclovir ± foscarnet for CMV
  - Corticosteroid to decrease the inflammation
  - IV immune globulin

Neurocysticercosis: Please also see Section 8.4

- Brain infection caused by helminthic worms.
- *Taenia solium* (pork tapeworm) causes most cases of neurocysticercosis.
- Other worms that infect brain are schistosomiasis, echinococcus multilocularis, Taenia multiceps, Taenia serialis, and Taenia brauni.
- Ingesting food contaminated with worm eggs, which are hatched to larvae and migrate to different tissue, including the brain forming a cyst.
- Death of worms causes local inflammation, edema, seizure, focal neurological deficit, and hydrocephalus.
- Rupture of cyst cause eosinophilic meningitis.
- Diagnosis:
  - CT or MRI → multiple calcified cystic lesions
  - CSF serology
  - Cyst biopsy
- Treatments:
  - Albendazole + Praziquantel + Dexamethasone for 2–4 days.
  - Praziquantel → alternate
  - Antiseizure meds
  - Surgical removal of the cyst.

9.4 Brain abscess

- Abscess or pus in the brain is usually due to focal necrosis and inflammation because of the extension of cranial infection or head wounds, dental infection, otitis media, or mastoiditis.
- Commonly caused by streptococcus ~70% followed by bacteroides, enterobacteriaceae, and staphylococcus.
- Other causes but less frequent are fungi, Toxoplasma gondii in AIDS patients, and parasitic infections.
- Sign and symptoms:
  - Headache, nausea, vomiting, seizure, personality change, ↑cranial pressure, progressive focal neurological deficit.
  - Mucor or Rhizopus infections cause frontal lobe abscess.

- Diagnosis:
  - Contrast enhanced MRI or CT → ring enhancing lesion.
  - Brain abscess due to Toxoplasma gondii in AIDS patients also has ring enhancing image on MRI.
- Treatment:
  - Ceftriaxone or Cefotaxime or Cefepime + metronidazole
  - Add Vancomycin if staph is suspected
  - Meropenem
  - Penicillin G + metronidazole
  - TMP-SMZ + Imipenem−Cilastatin for Nocardia ± Amikacin (if multiorgan involved) or Linezolid + Meropenem.
  - CT-guided aspiration
  - Surgical drainage
  - ± corticosteroids and antiseizure medications

9.5 Bacteremia

- Presence of bacteria in the blood (bacteremia), which may lead to immunological response (Sepsis).
- Caused by both gram-positive and gram-negative bacteria.
- Sign and Symptoms: fever, chills, shortness of breath, fatigue, anxiety, confusion, tachypnea, tachycardia, hypotension.
- Diagnosis: CBC with differential, BUN, electrolytes, liver panel, ABG, lactate, urinalysis, blood C&S, and chest X-ray.
- Treatment:
  - O2, ± intubation, IV fluids, ± vasopressors.
  - Vancomycin or Linezolid + anti-Pseudomonal Beta-lactam (Ceftazidime, Cefepime, Piperacillin-tazobactam, Meropenem, Imipenem)
  - Severe Penicillin allergy: Vancomycin + Ciprofloxacin or Aztreonam

9.6 Sepsis and septic shock

- Systemic inflammatory response of a whole body to infection.
- Infection caused by gram-positive and gram-negative bacteria results in the production of proinflammatory mediators.
- Release of cytokines and other proinflammatory chemicals cause dilation of arteries and arterioles, increase capillary permeability, leakage of fluid to interstitial compartment, decrease peripheral resistance, decrease blood pressure, hypoperfusion, metabolic acidosis, accumulation of lactic acid, failure of one or more organs, coagulopathy, altered mental status, and death.
- Septic shock → Sepsis + hypotension and no response on fluid resuscitation.

- Risk factors:
  - Bacteremia
  - Hospital stay → nosocomial infection
  - Recent surgery
  - Use of medical device
  - Infants or elderly >65
  - Pneumonia → most common cause of sepsis.
  - Chronic diseases
  - Genetic factors
- Diagnosis:
  - Clinical
  - CBC, ABG, BUN, liver, and kidney function tests
  - EKG and cardiac enzymes test
  - Blood culture
  - Systemic Inflammatory Response (SIRS): SIRS is a body response to whole body inflammatory state, which could be infectious or non-infectious. Two or more of the following criteria require further evaluation to identify sepsis.
    - Temp > 38°C (100,4 F) or < 36°C (96.8)
    - HR > 90
    - Respiratory rate > 20 or PaCO2 < 32 mm Hg
    - WBC count > 12,000/mcl, or < 4000, or > 10% bands (left shift)
  - Sequential organ failure assessment score (SOFA) and quick SOFA (qSOFA) score are used for mortality risk and measure dysfunctions of lung, liver, CVS, renal and CNS.
  - Quick SOFA score:
    - Respiratory rate > 22/min
    - Altered mental status
    - SBP < 100 mm Hg
    - Mortality is high if score is two or more in qSOFA score or increased from the initial score.
- Treatments
  - Fluid resuscitation
  - Pressors as needed
  - Empiric antibiotics based on suspected source of infection (Table 9.8).

Table 9.8 Choice of antibiotics in sepsis.

Source	Empiric choice of antibiotics	Comments
Unknown	Meropenem + vancomycin or daptomycin, or Ceftazidime-avibactam + vancomycin Aztreonam + vancomycin if allergy to PCN.	If ESBL suspected
Biliary	Piperacillin-tazobactam + vancomycin Piperacillin-tazobactam or ceftriaxone + metroni-dazole.	No ESBL suspected

9.7 Cardiovascular infection

9.7.1 Endocarditis

- Infective endocarditis: infection of the endocardium, including heart valves
- Most commonly caused by gram positive cocci (S. viridian or *S. aureus*), about 80% −90%. Other causes are gram-negative HACEK organisms or fungi.
- *S. aureus* usually causes acute bacterial endocarditis, which is developed and progresses abruptly and rapidly.
- *S. viridian* causes subacute bacterial endocarditis (SBE), which develops and progresses slowly.
- Mitral valves are involved in most of the cases. Tricuspid valves are involved in IV drug user
- Sign and Symptoms:
  - In acute endocarditis, sign and symptoms develops very fast, and within days patient condition become toxic and may progress to septic shock.
  - Fever and murmur are the most common presentation of endocarditis.
  - In Subacute bacterial endocarditis (SBE). Initial symptoms develop slowly Including low grade fever, weight loss, night sweating, and murmur and valvular insufficiency.
  - Other signs:
    - Roth spots: retinal emboli or hemorrhage
    - Osler nodes: painful erythematous nodules at the tips of digits.
    - Janeway lesions: splinter hemorrhages under nails and hemorrhagic macules on palms or soles which are nontender.
- Diagnosis:
  - Clinical
    - Suspects infective endocarditis in any patient with fever and murmur without obvious source of infection. Patient may have a history of IV drug use or a recent invasive procedure or have valvular heart disease.
  - Blood culture:
    - three blood cultures within 24 h or 2 cultures within 1−2 h if ABE is suspected.
    - Cultures will be positive if no empiric antibiotics are used.
  - Echocardiography
  - Duke criteria for Infective endocarditis (Table 9.9):
- Treatment:
  - Empiric treatment: start treatment with empiric antibiotics as soon as suspected endocarditis and blood sample is drawn in patients look severely ill.
  - Native valve and no history of IV drug use: Ampicillin + nafcillin + gentamycin or Vancomycin + gentamycin or ceftriaxone
  - Prosthetic valve: Vancomycin + gentamycin + rifampin

Table 9.9 Duke criteria.

Major criteria	Minor criteria
Two positive blood cultures for organism most commonly cause endocarditis.	IV drug user.
Three positive blood culture.	Predisposing heart problem.
Positive echocardiogram test.	Fever greater or equal to 38°C.
• Oscillation cardiac mass on heart valve(s)	Vascular sign and symptoms.
• Cardiac abscess	• Pulmonary embolism (septic)
• New sign of valvular regurgitation	• Intracranial hemorrhage
• New prosthetic valve dehiscence	• Arterial embolism
	• Mycotic aneurysm
	• Janeway lesions
	• Conjunctival petechiae
	Immunological sign and symptoms.
	• Glomerulonephritis
	• Osler nodes
	• Roth spots
	• Rheumatoid factor
	Infection consistent with microorganism causing endocarditis but not meeting major criteria.
	Serological positive test with microorganism cause endocarditis.

Definite Diagnosis = 2 major criteria or 1 major criteria + 3 minor criteria or 5 minor criteria.
Possible Diagnosis= 1 major criteria + 1 minor criteria or 3 minor criteria.

  - IV drug user: Nafcillin
  - Targeted antibiotics are chosen according to sensitivity test and adjusted according to the valve involved.

9.7.2 Noninfective endocarditis (marantic endocarditis)

- Accumulation of platelet and fibrin on cardiac valves and endocardium.
- Physical trauma during cardiac procedures, SLE, Antiphospholipid antibody syndrome, Liberman Sacks lesions, granulomatosis with polyangiitis.
- Complications: distal emboli result in infarction.
- Treatment
  - Anticoagulant and treating predisposing factors.
  - May require surgery
- **Dental procedure in high-risk patients**:
  - Prosthetic cardiac valve replacement
  - Previous history of infectious endocarditis
  - Congenital heart disease
  - Heart transplantation
  - Prophylaxis:
    - Amoxicillin 2 gm 1 h before procedure, Children 50 mg/kg

- Penicillin allergy → give Cephalexin 2 gm for adults, 50 mg/kg for children. Clindamycin 600 mg for adults, 20 mg/kg for children.

9.7.3 Myocarditis

- Inflammation of myocardium result in necrosis of myocytes cells.
  - Infection (Table 9.10)
  - Autoimmune disease
  - Drugs
  - Sarcoidosis
  - Idiopathic
- Sign and symptoms:
  - Varies from no symptoms to heart failure depending upon the severity and extent of inflammation.
  - S3, S4 gallops, muffled S1 sounds.
  - Friction rub, murmurs, ventricular enlargement to dilated cardiomyopathy.
  - Arrythmias and sudden cardiac death.
  - Fever, myalgia, dyspnea, ↓cardiac output.
- Diagnosis:
  - ECG
  - Cardiac Enzymes
  - Cardiac Imaging
  - Endomyocardial biopsy
  - Antistreptolysin- O titers for rheumatic fever
- Treatment:
  - Treat the symptoms like arrhythmias and heart failures.
  - Antibacterial and antiviral has not shown to be effective.
  - Parasitic infection can be treated with the appropriate antiparasitic agent.

Table 9.10 Etiology of infectious myocarditis.

Viruses (most common)	Bacterial	Fungus	Parasite
Coxsackie B virus	Staphylococcus sp.	Blastomycosis	Amebiasis
HIV	Group B streptococcus	Candidiasis	Chagas disease
Human herpes virus 6	Gram-negative bacilli	Coccidioidomycosis	Toxoplasmosis
Influenza virus	Lyme disease	Histoplasmosis parvovirus B19	Tuberculosis SARS-CoV-2

9.7.4 Pericarditis

- Inflammation of pericardial sac ± fluid accumulation.
- Causes

  - Infection
  - Trauma
  - Myocardial infarction
  - Tumors
  - Metabolic disorder
- Viruses are the most common cause of infective pericarditis.
  - Coxsackieviruses A and B, echovirus, adenovirus, parvovirus B19, HIV, influenza virus, and herpes virus
- Bacterial causes are
  - *Staphylococcus aureus*
  - *Strep. pneumoniae*
  - *N. meningitidis*
  - Enterobacteriaceae
  - *Mycobacterium tuberculosis*
- Fungal
  - *Histoplasma capsulatum,* Coccidiodes, Candida, and Blastomyces.
- Parasitic:
  - Echinococcus, Toxoplasma.
- Noninfectious:
  - Malignancy, connective tissue disorder, Uremia, and myxedema.
- Sign and Symptoms:
  - Pleuritic chest pain (may be relieved by sitting up and leaning forward).
  - Pericardia friction rub, ± muffled heart sound.
  - Dyspnea, tachypnea.
  - Fever, chill, and dry cough.
  - May result to cardiac tamponade which is manifested by hypotension, pulses paradox, pallor and clammy skin, jugular vein distention, ↓cardiac output.
  - Dressler Syndrome: delayed inflammatory response after myocardial infarction usually after several weeks result in pericarditis.
- Diagnosis
  - Clinical
  - Electrocardiography
  - Pericardiocentesis
  - Chest X-ray
- Treatment
  - Bacterial: Vancomycin + ceftriaxone or Cefepime
  - Replace to Daptomycin + Ciprofloxacin in case of allergies
  - Fungal: Itraconazole + prednisone
  - Tuberculosis: same regimen as the treatment of primary tuberculosis
  - Pericardiocentesis to remove the effusions
  - NSAID, colchicine, corticosteroid for pain and inflammation

9.7.5 Mycotic aneurysm

- Dilation of vessel wall due to infection.
- About 0.7%–3% aortic aneurysm are infectious in origin.
- Infectious aneurysm is mostly bacterial, but viral and fungal causes are also possible.
- Common pathogen responsible are
  - *Staph. aureus*
  - *Staph. epidermidis*
  - Salmonella species
- Risk factors:
  - IV drug user
  - Invasive procedure
  - Immunocompromised
  - History of endocarditis
- Sign and symptoms:
  - Fever, pain at the site of infection, headache
  - Pulsatile mass
  - Local expansion may result dysphagia, hoarseness, and hemoptysis.
  - Thrombosis, hemorrhage, rupture, stroke if cerebral aneurysms.
- Diagnosis:
  - Clinical
  - Imaging studies
  - Culture
- Treatment:
  - Vancomycin + Ceftriaxone or Piperacillin-tazobactam × 6–8 weeks.
  - Ciprofloxacin is the alternate if patient is allergy to B-lactam
  - Fungus: Micafungin or Caspofungin
  - Surgery

9.8 Urinary tract infection

1. Kidney (pyelonephritis)
2. Bladder (cystitis)

Sometime urethritis and prostatitis are also included in UTI.

- Bacterial infection is the most common cause of UTI.
- Less commonly caused by fungi, viruses and parasite.
- More common in women

- *E. coli* (75%–95%), Klebsiella, *P. mirabilis*, or *P. aeruginosa* are the major pathogens responsible for bacterial UTI.
- *S. saprophyticus*, *E. faecalis*, and *S. agalactiae* are less commonly involved.
- Adenovirus causes hemorrhagic cystitis
- Filariasis, trichomoniasis, leishmaniasis, schistosomiasis, and malaria are the parasitic causes of UTI.
- Bacterial UTI is divided into (Table 9.11):

Sign and symptoms (Table 9.12)

- Diagnosis:
  - Urine analysis
  - Urine culture in complicated UTI
  - Positive nitrite test (high specificity but low sensitivity).
  - Leukocyte esterase test (high specificity and good sensitivity)

Pyuria > 8wbc/uL in urine.
Culture:
Asymptomatic bacteriuria > 10^5/mL in men
Asymptomatic bacteriuria > 10^2/mL in women
Uncomplicated cystitis > 10^3/mL

Treatment (Table 9.13)

Table 9.11 Uncomplicated and complicated UTI.

Uncomplicated UTI	Complicated UTI
Premenopausal woman	Postmenopausal woman
No anatomical or functional abnormality	Abnormality present
Not pregnant	Pregnant
No comorbidity	Comorbidity
	Child

Table 9.12 Sign and symptoms of UTI.

9.8.1 Cystit*is*	9.8.2 Acute pyelonephritis	9.8.3 Urethritis
Frequency, urgency, and burning, nocturia, suprapubic, and back pain. Turbid urine with ± hematuria	Same as cystitis + fever, chill, flank pain, colicky abdominal pain with nausea and vomiting. Costovertebral angle tenderness on percussion.	Dysuria, purulent, whitish urethral discharge

Table 9.13 Treatment options for UTI.

Cystitis	Acute pyelonephritis	Complicated UTI
a) Bactrim DS or nitrofurantoin b) Fosfomycin c) Ciprofloxacin (2nd line)	a) Ceftriaxone IV b) Ciprofloxacin c) Cefepime if pseudomonas or resistant to previous therapy. d) Levofloxacin (second line due to high resistance)	Mild infection: a) Ciprofloxacin b) Ceftriaxone c) Levofloxacin Severe infection a) Cefepime IV or ceftazidime IV b) Carbapenem c) Vancomycin if h/o prior infection

9.8.4 Catheter associated UTI

- Positive culture (blood or Urine)
- Catheter in place >2 days.
- Sign and symptoms are nonspecific.
- May develop supra pubic discomfort, fever, malaise, altered mental status, flank pain.
- Treatment is the same as for complicated UTI.

9.8.5 Chronic pyelonephritis

- Recurrent acute pyelonephritis >3 episodes.
- Anatomical abnormality or calculi is the most common cause of recurrent episodes of pyelonephritis, and result in urinary reflux into the renal pelvis.
- Signs and symptoms are nonspecific.
- Diagnosis is made by urinalysis, urine culture, and imaging studies.
- Treatment consists of removing the obstruction or correction the anatomical abnormality and use of long term antibiotics.
- Choice of antibiotics: TMP-SMX, nitrofurantoin, or fluoroquinolone are used.

9.8.6 Fungal UTI

- Most commonly caused by Candida species.
- Other invasive fungi such as Aspergillus species, Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces species, and *Coccidiodes immitis* are capable of causing UTI.
- Most infections are asymptomatic
- Symptomatic infection may cause urethritis in men. Other symptoms are dysuria and watery discharge.
- Diagnosis is made by urine culture

- Symptomatic patients are treated with fluconazole.
- Resistant fungi are treated with amphotericin B + flucytosine

9.8.7 Prostatitis

- Inflammation of the prostate due to infection or other causes.
- Bacterial cause:
  - Enterobacteriaceae (mostly *E. coli*) 80%
  - Enterococci
  - *P. aeruginosa*
  - Chlamydia and Trichomonas in STD cases
- Sign and Symptoms:
  - NIH classifies prostatitis into four categories based on clinical symptoms and signs of infection in two urine samples. First sample is obtained as a midstream collection and second sample after massaging the prostate (Table 9.14).
    - **i)** acute bacterial prostatitis: Clinical symptoms fever, chill, incomplete bladder emptying, frequency and urgency, Prostate is tender, swollen, ± sepsis.
    - **ii)** Chronic bacterial prostatitis: Less severe than acute but most common cause of recurrent UTI in men.
    - **iii)** Chronic prostatitis/chronic pelvic pain syndrome: Pain is the most common symptom present during ejaculation, urinary irritation and obstruction.
    - **iv)** Asymptomatic inflammatory prostatitis: does not cause any symptoms. However, inflammation is present without infection.
- Risk factor
  - Invasive urethral procedure
  - Trauma
  - Old age
  - Bladder infection
- Diagnosis:
  - Urinalysis
  - Premassage and postmassage urinalysis except in acute prostatitis
  - Urine culture

Table 9.14 Category of prostatitis.

	WBC		Bacteria	
Category	**Premassage**	**Postmassage**	**Premassage**	**Postmassage**
i) Acute bacterial prostatitis	±	+	±	+
ii) Chronic bacterial prostatitis	±	+	±	+
iii) Chronic prostatitis/chronic pelvic pain syndrome.	−	+	−	−
iv) Asymptomatic inflammatory prostatitis	−	+	−	−

- Treatment:
  - Fluoroquinolone × 3–4 weeks
  - Ampicillin + gentamicin if sepsis
  - TMP-SMZ DS BID × 4–5 weeks

9.9 Gastro-intestinal infection

9.9.1 Mouth infection

- Thrush → most commonly caused by Candida sp.
  - White plaque on mucosal membrane, bleeding on scraping.
  - Usually seen in immunocompromise patients, use of antibiotics, transplant patients etc.
  - Treatment: Nystatin oral suspension or lozenges, fluconazole PO.

9.9.2 Gastroenteritis (infectious diarrhea) please also see Section 4.3

- Diarrheal disease is very common worldwide and is a major cause of morbidity and mortality in children under 5 years old. Most of the death in children is due to dehydration which can be preventable with hydration and electrolyte replacement.
- Classified into:
  - Acute <4 weeks Chronic >4 weeks
  - Inflammatory Noninflammatory
- Acute inflammatory diarrheal diseases are mostly viral in nature. Bacterial and toxin mediated or parasitic are less common.

9.9.2.1 Viral diarrhea: also see Section 6.4

- Rotavirus and norovirus, followed by astrovirus and adenovirus, are the most common viruses involved.
- Rotavirus causes diarrheal illness in very young children, especially in a daycare setting.
- Norovirus usually infect older children and adults, especially people on a cruise ship and nursing homes.
- Astrovirus infects people of all ages, mostly children under the age of two are infected the most. The same is true for adenovirus.
- Most infections are transmitted via fecal oral route, including contaminated food and water.
- Sign and Symptoms:
  - Viruses usually cause watery diarrhea with or without vomiting
  - Fecal blood, WBC or RBC are uncommon.
- Diagnosis:
  - Mostly clinical

  - Stool viral antigen
  - Nucleic acid test.
- Treatment:
  - Treatment for the viral diarrheal disease is mostly fluid and electrolyte replacement, oral or IV.

9.9.2.2 Bacterial diarrheal disease: also see Section 4.3.1

  - Commonly caused by:
  - *E. coli*
  - Salmonella
  - C. jejoni
  - Shigella
  - *C. difficile*
- *E. coli* causes several types of diarrheal disease depending upon the *E. coli* subtype.
  - Enterohemorrhagic (EHEC)
    - Cause bloody diarrhea
    - Produce Shiga like toxin
    - Undercooked beef, unpasteurized milk, and contaminated water are the primary source of infection
    - Can be transmitted person to person
    - 2%–7% of cases may lead to Hemolytic uremic syndrome.
  - Enterotoxigenic
    - Produce cholera like toxin
    - Cause watery diarrhea
    - Most common cause of traveler diarrhea
  - Enteropathogenic:
    - Not very common
    - Watery diarrhea in nurseries
  - Enteroinvasive:
    - Mostly common in the developing world
    - Cause bloody or nonbloody diarrhea
- Salmonella, *C. jejoni*, and shigella invade the mucosal wall and cause inflammation, which results in fever, cramping, and blood in stool.
  - Undercook poultry, unpasteurized milk, and contact with sick dogs and cats are the source of infection in humans.
  - Complication:
    - *C. jejoni*: about 30% of patients may develop Gillian–Bare–Syndrome or Septic arthritis
  - Shigella is associated with hemolytic-uremic syndrome
- *C. difficile* is a spore forming gram positive anaerobe which is associated with pseudomembranous colitis due to the use of antibiotics.

9.9.2.3 Diarrhea caused by exotoxins

- Staph aureus
- B. cercus
- *C. perfringens*
- Canned foods, rice dishes, meat, and vegetables are the most common source
- Cause acute watery diarrhea with ± nausea and vomiting

9.9.2.4 Parasitic infectious diarrhea

- Usually cause chronic diarrhea, with or without fever.
- Entamoeba histolytica causes bloody dysentery

- Diagnosis
  - Clinical
  - Stool testing
  - Serological tests. Antigen
- Treatment:
  - Assessment of dehydration
  - Fluid repletion
  - Empiric antibiotic for severely ill patients
  - For travel diarrhea cipro or Levaquin can be used
  - Metronidazole for parasitic infectious diarrhea
  - Oral Vancomycin or Fidaxomicin for *C. difficile*

9.9.3 Diverticulitis

- Inflammation of diverticula (outpouching of the intestinal wall).
- About 10%–25% of patients with diverticulosis present with diverticulitis.
- 25%–50% of patients may have a recurrent episode of diverticulitis.
- Mortality rate in uncomplicated diverticulitis is very low, while patients with complicated diverticulitis may have death rate ranging from 5% to 20%.
- Actual cause is unknown. However, it is thought that intestinal bacteria such as Enterobacteriaceae, Bacteroides, enterococcus species, and other inflammatory process or cytomegalovirus may be a cause.
- Risk factors:
  - Diet high in fat, red meat, and low fiber
  - Obesity
  - Smoking
  - Drugs such as NSAIDs, steroids, and opiates.
  - Nuts, seeds, and popcorn are NOT associated with increased risk of diverticulitis.
- Sign and symptoms:
  - Patient has left lower quadrant pain and tenderness. Patients of Asian descent may present pain on right side.

  - Nausea vomiting
  - Diarrhea or constipation.
  - May have fever, especially in patients with abscess and perforation.
  - May have urinary symptoms.
- Complications:
  - Approximately 15% of patients with acute diverticulitis may develop complications such as:
  - Formation of abscess
  - Formation of a fistula
  - Bowel obstruction and perforation.
  - Peritonitis
  - Sepsis
- Diagnosis
  - Abdominal and pelvic CT with or without water soluble contrast. MRI for pregnant women and children.
  - Typical CT findings will be bowel wall thickening, pericolic fat stranding, and pericolic fluid. Sensitivity and specificity of CT are around 97%.
  - Ultrasound can be used but sensitivity and specificity are lower than CT and highly depends on the operator.
  - Colonoscopy can only be used after the resolution.
  - Laboratory tests may show leukocytosis, ↑ESR and CRP.
- Differential diagnosis:
  - Cholecystitis
  - Mesenteric ischemia
  - Cholangitis
  - Constipation
  - Inflammatory bowel disease
  - Perforation
  - Bowel obstruction
- Treatment:
  - Liquid diet or NPO
  - Antibiotic that covers gram negative rods and anaerobic
  - Metronidazole + fluoroquinolone
  - amoxicillin-clavulanate for outpatient
  - Zosyn for mild to moderate disease
  - Meropenem for severe disease
  - Surgery

9.9.4 Appendicitis

- Acute inflammation of the appendix due to the obstruction of the lumen. Most common causes of obstructions are:

  - Lymphoid hyperplasia
  - Feces
  - Worm
  - Foreign body
- Risk factors:
  - Most commonly occurs between the ages of 5 and 45 years.
  - Family history
  - Cystic fibrosis
  - Men are at higher risk than females.
  - Pregnancy
- Sign and symptoms:
  - Right lower quadrant pain, or epigastric or periumbilical pain, rebound tenderness at McBurney point, fever, nausea and vomiting, anorexia.
  - Classic sign of appendicitis is present in less than 50% of patients. Atypical signs are common in pregnant and older patients.
    - McBurney's sign → tenderness at McBurney's point which is located 1/3 distance from the anterior superior iliac spine and belly button. Most of the time pain starts at belly button, moves to McBurney's point, and then to the right lower quadrant.
    - Rovsing's sign → Right lower quadrant pain by pressing left lower quadrant.
    - Psoas sign → Person lies on their left side and extension of right hip result in pain.
    - Obturator sign → flexing the hip and knee at 90 degrees while lying down and internally rotation cause pain.
  - The risk of rupturing the appendix varies, but tentatively it is about 2% at 36 hours and increases by 5% every 12 hours after first 36 hours.
- Complications:
  - Perforation
  - Peritonitis
  - Sepsis
- Diagnosis
  - Clinical
  - Abdominal CT
  - Ultrasound if pregnant or children
  - Laboratories value. ↑WBC and CRP. The possibility of appendicitis is very low with the normal values of WBC and CRP level, specificity is 98%. Increasing level of WBC and CRP is correlated with increased likelihood of complicated appendicitis.
  - Guarding and peritoneal sign could be signs of rupture appendix.
- Differential diagnosis:
  - Crohn's disease
  - Mesenteric ischemia

  - Ectopic pregnancy
  - Endometriosis
  - Kidney stone
  - Irritable bowel disease
  - Ovarian torsion
- Treatment
  - IV fluid
  - Pain medications
  - Surgery
  - Meropenem or piperacillin-tazobactam, Ceftriaxone + metronidazole.
  - Penicillin allergy → Ciprofloxacin or levofloxacin + metronidazole.
  - If appendix is perforated it will cause peritonitis which required immediate surgery with antibiotics → third-generation cephalosporin + metronidazole.

9.9.5 Peritonitis

- Inflammation of peritoneum, which may result in accumulation of fluid in peritoneal cavity called "Ascites."
- Classified into:
  - Primary peritonitis: Does not involve any other structure in the abdomen. If the infection is the cause, than it is called "Spontaneous bacterial peritonitis."
    - Gram negative → *E. coli, K. pneumonia,* Pseudomonas. 75% of cases involve gram negative bacteria (mostly *E. coli* or K. pneumonia).
    - *Streptococcus pneumoniae*, Staphylococcus species
  - Secondary peritonitis: Inflammation of peritoneum due to other structure involvement such as:
    - Perforation of bowel → Multiflora, Gran-negative and anaerobic bacteria, fungi (Candida)
    - Necrotizing pancreatitis
    - Cancer
    - Ruptured ectopic pregnancy
    - Peritoneal dialysis
    - Liver cirrhosis
- Sign and Symptoms
  - Generalized stomach pain, discomfort, ± diarrhea
  - Fever, peritoneal sign (rebound tenderness, guarding), pain increases with movement and breathing, patient lying very still with knees flexed.
- Risk factors:
  - Immunocompromised
  - Liver cirrhosis
  - Appendicitis
  - Pancreatitis

  - Renal disease
  - Peritoneal dialysis
  - Previous history of SBP
  - Long term use of proton pump inhibitors → promote gut bacterial growth and translocation.
- Complications:
  - Cardiovascular problem
  - Kidney failure
  - Liver failure
  - Intraabdominal abscess or fistula
  - Sepsis or septic shock
  - Death
- Diagnosis
  - Paracentesis → Exudate in nature (in case of fluid accumulation in the peritoneal cavity) (Table 9.15).
  - Complete blood count with differential
  - Serum-to-ascites albumin gradient (if greater than 1:1 and PMN or granulocytes greater than 500 cells/uL →SBP).
  - Imaging studies
  - Culture
  - Rapid reagent strip test (detect esterase in ascitic fluid).
- Differential diagnosis:
  - Perforated bowel
  - Pyelonephritis
  - Diverticulitis
  - Appendicitis
  - Mesenteric Ischemia
  - Abdominal abscess
- Treatment
- Third generation cephalosporin for SBP. Only ceftazidime cover pseudomonas.
- Fluoroquinolone for penicillin allergy
- Add metronidazole if perforation of bowel suspected

Table 9.15 Difference b/w exudate and transudate: LD = Lactate Dehydrogenase.

Paracentesis	Ascites/serum Protein ratio	Ascites/serum LD ratio	Ascites LD U/L	Neutrophils	PH	Glucose
Exudate	>0.5	>0.6	>400	>500 cell/uL	Low	Low
Transudate	<0.5	<0.6	<400	Few	Normal	Normal

9.10 Ear infection

9.10.1 Otitis media

Infection of the middle ear. Usually caused by viral or bacterial. Viral infection is usually followed by secondary bacterial infection. Type of bacteria involved varies with age group (Table 9.16).

- Viral cause includes: respiratory syncytial virus, influenza virus, parainfluenza virus, rhinovirus, and adenovirus.
- Most common pediatric diagnosis between the ages of 6–24 months. About 90% of children experience otitis media before school ages.
- Risk factors:
  - Smoking (family member)
  - Family history
  - Bottle feeding
  - Daycare
  - Immunocompromised
  - Anatomical abnormalities
  - Ciliary dysfunction
  - Vitamin A deficiency
  - Allergies
  - Low socioeconomic status
- Complications:
  - Mastoiditis
  - Petrositis or labyrinthitis
  - May cause conductive hearing loss
  - Meningitis or brain abscess
  - Hydrocephalus
- Sign and symptoms:
  - Earache
  - Fever
  - Nausea and vomiting, +/− diarrhea
  - Neurological symptoms if spread to intracranial space.
- Diagnosis:
  - Clinical evaluation
  - Otoscopy exam → bulging, erythematous, and decreased mobility of tympanic membrane.

Table 9.16 Bacteria responsible for otitis media.

Neonate	Children <14 year	Children >14 year and adults
E.Coli	Strep. pneumoniae	Strep. pneumonia
Staphylococcus aureus	Moraxella catarrhalis	Group a hemolytic strep hemophilus influenza staph. aureus H. influenza

  - Tympanocentesis
  - Culture
- Differential diagnosis:
  - Cholesteatoma
  - Fever
  - Nasopharyngeal tumor
  - Otitis externa
  - Mastoiditis
  - Teething
- Treatment:
  - Pain and fever reliever
  - Decongestants and antihistamines may be helpful
  - +/− antibiotics → 80% of cases resolved themselves, use of antibiotic help in faster recovery.
- Choice of antibiotics:
  1. Amoxicillin
  2. Cephalosporin for penicillin allergies
  3. Augmentin for resistance cases
  4. Levofloxacin (adults) Clindamycin for children or adults
  5. Azithromycin

9.10.2 Mastoiditis

- Infection of mastoid air cells usually secondary to otitis media.
- Mostly affects children of ages 2 years or less.
- Group A beta-hemolytic streptococcus, *Staphylococcus aureus*, Streptococcus pyogenes, and Hemophilus influenzae are common bacteria involved.
- Risk factors:
  - Age 2 years or younger
  - Recurrent acute otitis media
  - Cholesteatoma
  - Immunocompromise
- Sign and symptoms:
  - Same as acute otitis media plus tenderness, swelling, and erythema behind the ear.
  - Lethargy, fever, nausea, and hearing loss may be present.
  - Pinna may be displaced.
- Diagnosis:
  - Clinical
  - CT
  - Tempanocentesis for culture.

- Differential diagnosis:
  - Cellulitis
  - Otitis externa
  - Trauma
  - Tumor
  - Lymphadenopathy
- Treatment:
  - First choice: IV ceftriaxone, or Cefotaxime
  - Second choice: Vancomycin
  - Mastoidectomy

9.10.3 Otitis externa (swimmer's ear)

- Infection of external ear canal
- Most commonly caused by *Pseudomonas aeruginosa* or *Staphylococcus aureus*.
- Other bacteria, such as *E. coli*, and fungus infection are less common.
- Most of the cases of otitis externa occur during summer and in the tropical climate. Affect all age group.
- Pathophysiology of otitis externa is believed to be disruption of acidic PH, loss of protective wax, damage to the epithelium, accumulation of moisture, and growth of bacteria.
- Can be classified into:
  - Acute <6 weeks
  - Chronic >3 months
- Risk factors:
  - Swimming
  - Humidity
  - Trauma
  - Narrow external ear canal
  - Foreign body obstruction
  - Mechanical cleaning (cotton swab).
  - Diabetes
  - Immunocompromised
- Sign and symptoms:
  - Pain and drainage
  - Hearing loss
  - Posterior auricular lymphadenopathy.
- Complications
  - Malignant otitis externa → osteomyelitis of temporal bone
- Diagnosis:
  - Clinical
  - Hearing tests
  - Gram stain and culture.

- Differential diagnosis:
  - Contact dermatitis of the external ear canal
  - Acute otitis media
  - Herpes zoster oticus
  - Furunculosis
  - Temporomandibular joint infection
- Treatment:
  - Debridement
  - Topical acetic acid to change the PH to more acidic
  - Topical corticosteroid to decrease the inflammation
  - Topical antibiotics → Cipro, Ofloxacin, Neomycin
  - For fungal infection → Nystatin or clotrimazole topical solution.

9.11 Nasal infection

- Most commonly caused by Staphylococcal aureus
- 20% people has *Staphylococcus aureus* as part of their normal nasal flora
- Intranasal mupirocin or bacitracin can be used, but reoccurrence is common.

9.12 Eye infections

9.12.1 Conjunctivitis (Fig. 9.6)

FIGURE 9.6 Conjunctivitis.

- Inflammation of the conjunctiva also called pink eye. Most cases are viral.
- Transmission of infectious conjunctivitis is usually hand to eye, contact with infectious tears, eye discharge, fecal matter or respiratory discharge, close contact, and sharing contaminated towels and linens.
- Conjunctivitis can be classified into (Table 9.17):
  - Viral conjunctivitis
  - Bacterial conjunctivitis
  - Allergy conjunctivitis

Table 9.17 Clinical Differences in acute conjunctivitis.

Symptoms	Bacterial	Viral	Allergic
Discharge	Thick, mucus, yellowish, PMN cells Foreign body sensation.	Watery, thin, clear, with mononuclear cells	Watery, thin, clear, with mostly eosinophils cells
Eyes	Usually affect one eye	Usually affect one eye	Both eyes are affected
Itching	None	None	Yes
Eyelid edema	Yes	Yes/no	Yes
Node involvement	None	Yes (preauricular lymphadenopathy)	None
History	None	History of recent upper respiratory tract infection.	History of allergies

9.12.1.1 Viral conjunctivitis

- Clear watery discharged, unilateral node usually involved, no itching. Irritation and foreign body sensation, and photophobia are commonly present.
- 90% of cases are caused by adenovirus. Rest are caused by enterovirus, HSV, and COVID-19.
- Most cases of viral conjunctivitis are self-limited and does not require antiviral except conjunctivitis caused by herpes simplex virus or varicella-zoster virus.
- Epidemic keratoconjunctivitis is a severe form of conjunctivitis which may lead to blindness, and caused by adenovirus serotype 8,19, and 37.
- Acute hemorrhagic conjunctivitis is a very contagious form of viral conjunctivitis which is most commonly associated with enterovirus 70, coxsackievirus A24, and adenovirus associated with epidemic worldwide in tropical and subtropical regions. Symptoms include redness, foreign body sensation, eyelid edema, conjunctival chemosis, and subconjunctival hemorrhage.
- Diagnosis:
  - Clinical
  - Nucleic acid amplification test (NAAT)
- Treatment:
  - Mostly supportive
  - Corticosteroids drop can be used to decrease inflammation but should not be used if HSV keratitis is suspected.
  - Povidone-iodine eye drops.
  - Antiviral eye drops in case of HSV

9.12.1.2 Bacterial conjunctivitis

- Purulent discharge, usually unilateral, severe eyelid edema. Photophobia. Lymph nodes involvement is absent.

- Commonly caused by *Staph. aureus, Strep. Pneumoniae, Hemophilus, Moraxella catarrhalis.*
- In children *H. influenzae*, *Strep. pneumoniae*, and *M. catarrhalis* are common pathogens.
- In contact lens wearers, usually gram-negative bacteria are associated for conjunctivitis. Pseudomonas in hospitalized critically ill patients.
- Less commonly is caused by gonococcal infection which develops 12–48 h after exposure, while neonatal gonococcal infection appears 2–5 days after delivery.
- Neonatal chlamydial eye infection usually appears 5–15 days after delivery.
- Complications
  - Corneal ulceration
  - Abscess
  - Perforation
  - Blindness
- Diagnosis:
  - Clinical
  - Culture
- Treatment:
  - Nongonococcal and nonchlamydial infections can be treated with ophthalmic drops such as Moxifloxacin, ciprofloxacin, trimethoprim/polymyxin.
  - Gonococcal and chlamydial infection, IM ceftriaxone, and oral or IV azithromycin plus gentamicin ophthalmic eye drop.
  - Newborn at the time of birth, prophylactically given erythromycin ophthalmic ointment to prevent the infection.

9.12.1.3 Allergic conjunctivitis

- Affects about 40% population.
- Can be acute, seasonal, and perennial
- Associated with IgE mediated hypersensitivity (typ1) reaction.
- Clear watery discharge with itching are most common symptoms and usually affects both eyes.
- Pain, decreased visual acuity, eyelids edema is not associated.
- Treatment:
  - Antihistamine eyedrops
  - May need corticosteroid eye drops for severe cases.

9.12.2 Stye (hordeolum)

- Bacterial infection of the sebaceous gland of eyelids (Fig. 9.7).
- Most commonly caused by *Staphylococcus aureus* followed by *Staphylococcus epidermidis.*

FIGURE 9.7 Stye.

- Present as a painful, red lump with pus. Usually localized to eyelid margin or under the conjunctiva.
- Fever or chill may be present
- Should be differentiated from chalazion which is a noninfectious obstruction of meibomian gland.

Diagnosis

- Clinical

Treatment

- Warm compress
- Drainage, +/− antibiotics→ oral cephalosporin, dicloxacillin, TMP-SMX

9.12.3 Blepharitis (Fig. 9.8)

- Inflammation of eyelashes follicles or eyelid margins
- Acute form is usually infectious and chronic form is noninfectious (seborrhea, rosacea, dry eye, meibomian glands dysfunction)

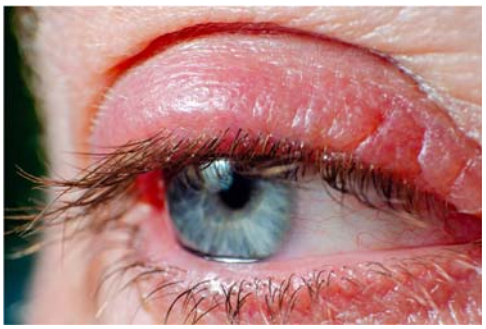

FIGURE 9.8 Blepharitis.

- *S. aureus* and *S. epidermidis* are the most common bacteria involved.
- Sign and symptoms:
  - Itching, burning, lacrimation, photosensitivity,
- Diagnosis;
  - Slit lamp examination
- Treatment
  - Warm compress
  - Artificial tears
  - ± Topical eye antibiotics

9.12.4 Dacryocystitis (Fig. 9.9)

FIGURE 9.9 Dacryocystitis.

- Infection of the lacrimal sac.
- Most common cause is *Staphylococcus aureus* or streptococcus species.
- Present with pain, edema, and redness around the lacrimal sac.
- Diagnosis
  - Clinical
- Treatment:
  - Warm compress.
  - Antibiotics
    - First choice: Cephalexin, amoxicillin-clavulanate
    - Second choice: TMP-SMX
    - Third choice: Vancomycin
  - Surgery

9.12.5 Uveitis

- Inflammation of iris, ciliary body, and choroid. Anterior chamber, vitreous fluid, and retina may also involve.
- Causes of Uveitis:
  - Infection
  - Idiopathic→ most common
  - Trauma
  - Autoimmune

- Sign and symptoms:
  - pain
  - Redness
  - Photophobia
  - Floaters
  - Decrease vision

CMV is the most common cause of uveitis in immune compromised patients. Toxoplasmosis is the most common cause in immunocompetent

Infectious Uveitis: Classified into.

- **Anterior uveitis:**
  - involved anterior chamber of the eye. Herpes simplex virus, Varicella–Zoster virus, and Cytomegalovirus are implicated in infections anterior uveitis
  - Pain, redness, photophobia, and decreased vision are common symptoms.
- **Intermediate uveitis:**
  - involve intermediate part of the eye chamber. Tuberculosis, Syphilis, and Lyme disease are mostly responsible.
  - Symptoms: Usually painless, floaters are common (snowball) and decrease vision.
- **Posterior uveitis:**
  - Involve posterior chamber of the eye. Toxoplasmosis, CMV, HSV, and VZV are infectious causes.
  - Symptoms: floaters, decrease vision, retinal vasculitis, yellow-white lesion on the retina, and optic disc edema.

- Diagnosis:
  - Slit-lamp exam
  - Ophthalmoscopy
  - Intraocular pressure
  - Antibody titers/serological test
- Treatment:
  - +/− Topical corticosteroid, depending upon the cause of uveitis
  - Cycloplegic mydriatic drops
  - Pyrimethamine, sulfonamide, or clindamycin for toxoplasmosis
  - Acyclovir, or valacyclovir for HSV and VZV
  - Ganciclovir, valganciclovir, or intravitreal foscarnet for CMV.
  - Penicillin G IM for syphilis.
  - Surgery → vitrectomy

Shining light in unaffected eye cause a pain in effected eye. This differentiates uveitis from conjunctivitis

9.12.6 Keratitis: → see in viral Section 6.11.1

- Inflammation of the cornea, which results in infiltration of inflammatory cells.
- Keratitis could be infectious and noninfectious
- Infectious causes are:
  - Bacterial: Staphylococcus, streptococcus, Pseudomonas, Moraxella, Nocardia, and Mycobacteria (atypical).
  - Viral: Herpes simplex virus (HSV), Herpes zoster virus, Adenovirus, and several other viruses associated with cold and flu.
  - HSV cause characteristic dendritic corneal ulcer.
  - Protozoa: Acanthamoeba, See Section 8.2.2.1.
  - Fungal: Aspergillus, Candida, Cladosporium, and Microsporidia.
- Noninfectious causes are
  - Foreign body, trichiatic eyelashes, and giant papillae.
  - Collagen, vascular, and autoimmune disease
  - Neurotropic corneal ulcer
  - Xerophthalmia.
- Sign and Symptoms:
  - Pain, redness, photophobia, lacrimation, foreign body sensation, ulceration, and permanent scarring.
- Diagnosis:
  - Slit-lamp exam
  - Ophthalmoscopy
  - Corneal scraping for microscopic exam and culture.
  - Serology
- Treatment:
  - Bacterial:
    - Ciprofloxacin or levofloxacin ophthalmic drops
    - Tobramycin or Gentamicin ophthalmic drops
  - Viral (Fig. 9.10):
    - HSV → Trifluridine ophthalmic drops
    - VZ → Famciclovir or Valacyclovir oral
    - Adenovirus: Symptomatic treatment.
  - Fungal:
    - Natamycin ophthalmic drops
    - Amphotericin B ophthalmic drops.
    - Itraconazole oral
    - Amphotericin B, Itraconazole, Voriconazole IV's

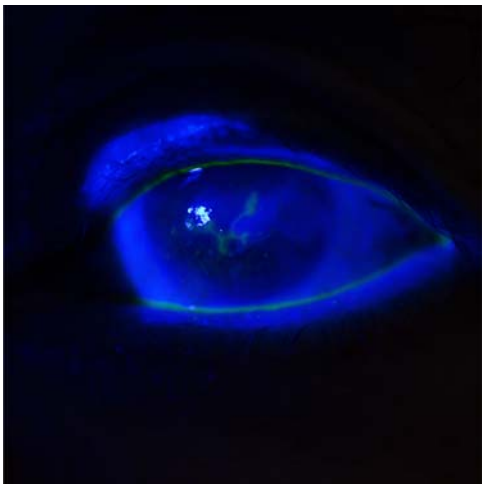

FIGURE 9.10 Herpes keratitis.

- Acanthamoeba:
  - Ophthalmic 0.02%–0.2% biguanide chlorhexidine
  - Polyhexamethylene biguanide 0.02%–0.06% + hexamidine or propamidine ophthalmic drops.

9.12.7 Cavernous sinus thrombosis (CST)

- Thrombosis in the cavernous sinus.
- Rare complication of nasal furuncle, bacterial sinusitis, or dental infection
- Pathogens responsible are *Staphylococcus aureus* followed by Streptococcus species and anaerobe.
- Sign and Symptoms:
  - Severe facial pain or unilateral headache, high fever, papilledema, photophobia, and vision loss.
  - If the infection spreads to CNS, it causes confusion, seizure, and focal neurological symptoms.
  - Cranial nerve third, fourth, fifth (ophthalmic and maxillary branch), and sixth cranial nerve passes near the cavernous sinus are affected and cause cranial nerve deficit
- Complications:
  - Brain abscess
  - Blindness
  - Meningoencephalitis
  - pituitary insufficiency
  - stroke

Sixth cranial nerve palsy is common in CST

- Diagnosis:
  - Clinical → Proptosis, ptosis, chemosis and cranial nerve palsy
  - MRI/CT
- Treatment: IV antibiotic, +/− corticosteroid
- Surgical drainage
- Anticoagulants usually are not used
- Choice of antibiotics:
  - Nafcillin or Oxacillin + ceftriaxone (third-generation cephalosporin) for MSSA
  - Substitute vancomycin if MRSA is suspected
  - Add metronidazole if anaerobe is suspected

9.12.8 Orbital cellulitis

- Inflammation of orbital tissue behind the orbital septum.
- Main cause is the infection spread from nasal sinuses, dental, or wounds.
- Streptococcus pneumoniae, *Staphylococcus aureus*, and S. pyogenes are the main pathogens depending upon the initial site of infection
- Sign and Symptoms: Pain in eye movement, eyelid swelling, bulging of the infected eye, decrease vision, ± fever.

Orbital cellulitis does not have cranial nerve deficit which is common in CST.

- Diagnosis:
  - Clinical
  - MRI/CT with contrast
- Treatment:
  - Admit the patient to a hospital
  - Treat with meningitis dosing of antibiotics
  - Ceftriaxone or cefotaxime, Zosyn, or meropenem
  - Add Vancomycin if MRSA is suspected
  - Add metronidazole if anaerobes
  - Surgery to decompress if:
    - Vision is affected
    - Pus or abscess
    - Foreign body
    - Antibiotics failed

9.12.9 Preseptal or periorbital cellulitis

- Inflammation and infection of the eyelid and skin around the eye anterior to the orbital septum.
- Tenderness, swelling of eyelid, redness, and warmth. However, intact eye functions, no pain in eye movement, or decrease in vision, and no proptosis
- Diagnosis: Clinical, MRI or CT
- Treatment:
  - Oral antibiotics → Clindamycin, Bactrim DS, Doxycycline

9.13 Skin infection

- Normal skin flora: *S. epidermis, S. aureus*, micrococci, diphtheroid, gram negative bacilli.

9.13.1 Folliculitis, furuncle, and Carbuncle

- Involve hair follicles
- Folliculitis is inflammatory nodules or pustules surrounding hair follicles. Usually, it itches with mild pain (Fig. 9.11)
- Furuncles are tender nodules or pustules involve hair follicles.
- Carbuncles are clusters of interconnected furuncles, which are painful, and filled with pus and a patient may have a fever
- Most commonly caused by *Staphylococcus aureus*. However, Pseudomonas aeruginosa is associated with hot tub folliculitis
- Diagnosis:
  - Clinical
  - Culture
- Treatment
  - Folliculitis → 1% clindamycin topical solution or oral cephalosporin
  - Furuncles and Carbuncles → Drainage, +/− antibiotic
  - TMP/SMX, Clindamycin, Doxycycline, vancomycin.

FIGURE 9.11 Folliculitis.

9.13.2 Ecthyma and impetigo

- Commonly caused by *S. aureus* or *S. pyogenes*
- Ecthyma is the ulcerative form of impetigo. Shallow punch out ulcer with a thick brown black crust
- Impetigo is classified into:
- Bullous impetigo:
  - Painful pustules or fluid filled vesicle grows rapidly and become bullae which rupture and cover with honey color crust.
- Nonbullous impetigo (Fig. 9.12)
  - Cluster of vesicles, which usually develop on previously damaged skin. They burst easily and cover with honey-colored crust.
- Symptoms: Itching with mild pain or discomfort
- Diagnosis: Clinical
- Treatment:
  - Topical mupirocin, bacitracin
  - Oral antibiotics → dicloxacillin, cephalexin, TMP-SMX, clindamycin, doxycycline.

FIGURE 9.12 Impetigo (non-bullous).

9.13.3 Erythrasma

- Cause by Corynebacterium minutissimum and mostly infects diabetic patients in warmer climates.
- It is usually confined to the third and fourth web space of foot.
- May also involve groin, axilla, or abdominal folds
- Characteristic coral red color under wood light and absence of hyphae in skin scraping when treated with hydrogen peroxide. This differentiates it from fungus infection.
- Treatment: Clarithromycin or topical erythromycin, clindamycin is the drug of choice.

9.13.4 Cellulitis (Fig. 9.13)

- Infection involves epidermis and dermis.
- Most commonly caused by Staphylococcus. aureus or Streptococcus pyogenes.
- Less commonly involved bacteria are S. agalactiae in old diabetic patients, Hemophilus influenza in children, Pseudomonas aeruginosa in diabetic or neutropenia patients or hot tub or spa patients. Pasteurella species for cat or dog bite. In immunocompromise patients, gram-negative bacteria can be involved.
- Sign and Symptoms: Red, warm, and painful. Borders are irregular, swollen, +/− fever and regional lymphadenopathy usually on the affected site.
- Streptococcus infection is diffuse and rapidly spread, while staphylococcal infection is localized
- Risk factors → recent surgery, trauma, animal bites, fungal, or viral infection
- Differential
  - Stasis dermatitis → usually bilateral, and itching
  - Erysipelas → distinct margins, superficial cellulitis
  - Deep venous thrombosis → skin temperature and color normal
- Diagnosis:
  - Clinical/physical exam
  - Blood culture→ patient with systemic symptoms or immunocompromise
  - Tissue culture→ not very helpful.
- Treatment (Table 9.18):

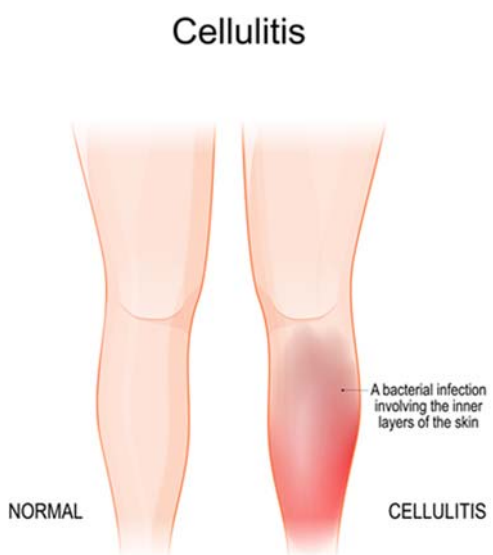

FIGURE 9.13 Cellulitis.

Table 9.18 Treatment options for cellulitis.

	First choice	Second choice
Mild infection	Cephalexin, amoxicillin	Azithromycin, SMZ/TMP, linezolid outpatient
Mammal bite	Amoxicillin/clavulanate	Clindamycin + fluoroquinolone
Inpatient	IV cefazolin, ceftriaxone	Oxacillin or nafcillin
MRSA	Vancomycin	Linezolid, daptomycin

9.13.5 Erysipelas

- Superficial cellulitis does not involve fat tissue.
- Same pathogens are involved, which cause cellulitis.
- Symptoms:
  - Shiny, raised tender rash with distinct margin, mostly on the face.
  - Fever, chill, and malaise may be present.
  - Orange peel appearance.
- Diagnosis: Clinical
- Treatment: Same as cellulitis. However, MRSA is usually not involved

9.13.6 Necrotizing soft tissue infection (NSTI)

- Involve all layers of skin, plus fat tissue and facia.
- Polymicrobial aerobic and anaerobic organisms are involved.
- Small vessel occlusions due to infection result in tissue infarction and necrosis.
- Sign and symptoms:
  - Severe pain, hot, swollen, red tissue which rapidly progresses to bullae, crepitus due to gas in soft tissue, and gangrene
  - High fever, tachycardia, hypotension, and change in mental status
  - Patient may develop septic shock and multiorgan failure
- Diagnosis:
  - Clinical
  - Blood and wound culture
  - CBC, inflammatory marker
  - X-ray of soft tissue shows gas
  - CT or MRI
- Treatment:
  - Emergent surgical exploration
  - Antibiotics (Table 9.19)

Table 9.19 Treatment option for NSTI.

1st choice	2nd choice
Vancomycin + piperacillin/tazobactam	Ceftriaxone + metronidazole
Or	Or
Linezolid + piperacillin/tazobactam	Fluoroquinolone + metronidazole or daptomycin + piperacillin/tazobactam

- IV fluids
- +/− Hyperbaric Oxygen

If NSTI suspected, do not wait for labs. Immediately prepare for surgical exploration.

9.13.7 Staphylococcal scalded skin syndrome (SSSS)

- Caused by staphylococcal toxin called epidermolysin
- Epidermolysin targets desmoglein-1 on epidermis and causes exfoliation.
- Most commonly affects newborns and children.
- Sign and symptoms:
  - Infection starts with a superficial lesion which is crusted and soon becomes painful, large, flaccid blister, fluid filled bullae, and quickly spread to other areas.
  - Bullae and blister easily rapture with gentle pressure (Nikolsky sign)
  - Widespread epidermis peeling results in sepsis and fluid loss.
  - Fever, chill, and malaise are common
- Diagnosis:
  - Clinical examination
  - Biopsy → shows superficial splitting of the epidermis
  - Culture→ should be taken from the area of primary infection. Bullae are sterile and do not yield any pathogen
- Differential diagnosis:
  - Toxic Epidermal Necrolysis (TEN) → usually infects older patient, and patient has a history of drug use. Absence of Nikolsky sign as it affects between epidermis and dermis.
- Treatment:
  - Treat in a burn unit
  - Gel dressing
  - Antibiotics
    - Nafcillin → Methicillin sensitive staph
    - Vancomycin or linezolid, or daptomycin → MRSA
  - Antistaphylococcal antibiotics like Nafcillin
  - Vancomycin if MRSA suspected

Avoid corticosteroid in SSSS syndrome.
Treat in burn unit.

Note: SSSS syndrome usually affects children and does not involve mucosa, while Toxic Epidermal Necrolysis TEN) affects older patients, and Steven Johnson Syndrome involves mucosal membrane.

9.13.8 Necrotizing fasciitis

- Infection that causes necrosis of subcutaneous tissue and muscle fascia.
- Medical emergency, immediate treatment is required
- Usually caused by mixed aerobic and anaerobic bacteria. Gram-positive cocci, such as *Staphylococcus aureus* and Streptococcus species, are responsible for the majority of the cases.
- Area is usually red, hot and swollen.
- Pain is out of proportion and patient looks severely ill
- TX: Surgical debridement and antibiotics IV (ceftriaxone or Pen G + clindamycin

9.13.9 Parasitic skin infection

9.13.9.1 Scabies (Fig. 9.14)

- Caused by *Sarcoptes scabiei* → obligate human parasite
- Lives in a burrowing tunnel in the stratum corneum
- Transmission
  - Person to person
  - Animal to person
  - Fomites
- Risk factors
  - Crowded environment
  - Unhygienic condition
- Sign and symptoms
  - Intense pruritis, erythematous papules usually appear on skin folds such as finger web space, wrist (flexor), elbow, buttocks, breast, and penis.
  - Burrows visible by naked eyes and is a classical sign.
- Diagnosis
  - Clinical
  - Scraping of the burrow
- Treatment
  - Permethrin
  - Lindane (not available in the United States)
  - Oral ivermectin.

FIGURE 9.14 Scabies source CDC (PHI).

9.13.9.2 Lice (Figs. 9.15 and 9.16)

- Classified into
  - Heal lice → Pediculus humanus capitis
    - Infest head
  - Body lice → *Pediculus humanus corporis*
    - Live in clothing and suck blood from the human body
    - Common vector of spreading epidemic typhus, trench fever, and relapsing fever
  - Pubic lice → *Pediculosis pubis*
    - Infest pubic area. Sexually transmitted
  - Transmission
    - Poor hygiene
    - Close contact
    - Fomites
  - Sign and symptoms
    - Intense pruritis, redness, scratches, urticarial, and secondary infections
  - Diagnosis
    - Clinical

FIGURE 9.15 Pediculus humanus.

FIGURE 9.16 Head lice's eggs. *Source: CDC (PHIL).*

- Treatment
  - Head lice
    - Topical permethrin 1%–5% (5% is not more effective than 1%)
    - Malathion 0.5%
    - Spinosad 0.9%
    - Ivermectin 0.5%
  - Body lice
    - Permethrin 5% cream
    - Ivermectin
  - Pubic lice
    - Permethrin 1% cream
    - Malathion 0.5%
    - Ivermectin oral × 1, repeat in 1 week

9.13.9.3 Bedbugs

- *Cimex lactularis and Cimex hemipterus* are responsible species.
- Lives in cracks, corners and crevices of mattresses, bedframes, and other furniture
- Bug bite results in sign of bites, purpuric, erythematous macules, papules that may or may not itch or may result in bullae.
- Diagnosis
  - Clinical
- Treatment
- Clean the bed, wash all the bedsheets and other covers with very hot water.
- Spray insecticides
- Topical corticosteroids over the bite
- Oral antihistamine

FIGURE 9.17 Cutaneous larva migrans. *Source: Wikipedia commons.*

9.13.9.4 Cutaneous larva migrans (Fig. 9.17)

- Hookworm infestation of the skin caused by dogs and cat's hookworm
- *Ancylostoma braziliense* is the dog hookworm most commonly involved.
- Ova are secreted in the feces and develop into larvae in warm and moist ground and infect humans by direct skin contact with the contaminated soil.
- Present worldwide.
- Sign and symptoms
  - Intense pruritis, erythema, and papules with inflamed threadlike migratory trail
  - May result secondary bacterial infection
- Diagnosis
  - Clinical
- Treatment
  - Thiabendazole 15% cream topical
  - Albendazole × 3–7 days
  - Ivermectin × 1–2 days.

9.13.9.5 Cutaneous myiasis (Figs. 9.18 and 9.19)

- Larvae (maggot) of various flies such as *Dermatobia hominis, Cardylobia anthropophagia,* and Cuterebra species lays eggs on insect and insect transfer eggs to human skin, where they are hatched and burrows into the skin
- Produce inflammatory response including itching and pain
- Secondary bacterial infection followed
- Treatment
  - Manual removal
  - Ivermectin × 1

FIGURE 9.18 Larvae borrow into the skin.

FIGURE 9.19 Larvae (Maggots). *Source: CDC (PHIL).*

9.14 Bone Infection

9.14.1 Osteomyelitis

- Inflammation and destruction of the bone due to infection
- Pathogens
  - *S. aureus* → most common. Other bacteria involved are enterics and Streptococcus sp.
  - E.coli and Group B Streptococcus are common in newborn babies.
  - IV drug user → *S. aureus*, S. Pseudomonas, Serrata sp, Candida sp.
  - Sickle cell disease, immune-compromised → Salmonella
  - Fungi, mycobacterium sp. → immune-compromised or in the endemic area.
  - Pott disease is chronic osteomyelitis caused by *M. tuberculosis* and involves lumber vertebrae.

- Risk factors
  - Orthopedic surgery, infected prosthetic joints
  - Trauma, deep infected wounds
  - Obesity
  - Diabetes,
  - IV drug user
  - Sick cell disease
  - Vascular insufficiency
  - Immuno-suppress patients
- Sigh and Symptoms:
  - Acute: Localized pain, swelling, and redness. Fever, malaise, fatigue, weight loss
  - Chronic: Intermittent bone pain, swelling, and draining sinuses
- Diagnosis:
  - ESR, CRP and CBC
  - X-rays, CT, MRI, nuclear imaging → Codman triangle→ raised periosteum
  - Bone culture or blood culture
- Treatment:
  - Nafcillin or Oxacillin + Ceftazidime or Cefepime for MSSA.
  - Use vancomycin if MRSA is suspected.
  - Daptomycin or Aztreonam or Ciprofloxacin if severe allergies.
  - Treatment should be continued for 6–8 weeks.
  - Surgery if no response to antimicrobial agents.

9.14.2 Septic arthritis

- Inflammation or infection of synovial or periarticular joints.
- Classified into gonococcal and nongonococcal infectious arthritis.
- Gonococcal infectious arthritis is caused by N. gonorrhea and mostly infects young adults.
- Nongonococcal infectious arthritis is further classified into acute and chronic.
  - Acute form developed in hours to a few days and is most commonly caused by *S. aureus*. However, gram negative bacteria and viruses may also be involved. Infect any age group.
  - Chronic form which is usually developed over weeks and caused by mycobacteria, fungus, or bacteria
- Risk factors:
  - Same as for osteomyelitis
- Sign and Symptoms
  - Gonococcal: Fever, migratory arthralgia, arthritis, and multiple small joints are involved. However, axial skeleton joints are rarely involved
  - Skin lesions on trunks and extremities

  - Nongonococcal: mild to severe pain in the involved joints, red, swollen, and warm joint. Usually involve one or two large joints such as knee, ankle, wrist, or hip. Fever is usually mild to non, and no skin lesions are present.
- Diagnosis:
  - Arthrocentesis and culture
  - PCR
  - CBC and ESR or C-reactive protein
  - X-ray, CT, MRI
- Treatment:
  - Gonococcal → Ceftriaxone + Azithromycin. Alternate: Azithromycin + Gentamicin
  - Nongonococcal:
    - ➢ Nafcillin
    - ➢ Cefazolin
    - ➢ Vancomycin, or Daptomycin if MRSA is suspected.
    - ➢ All treatments continue for 3–6 weeks.
    - ➢ Viral infection is treated supportively.
    - ➢ Fugal with antifungal.

9.14.3 Prosthetic joint infection

- Classified into acute and chronic infection.
- 2/3 prosthetic joint infections developed within a year of surgery.
- *S. aureus* and *S. epidermidis* are the most common bacteria involved than gram-negative and anaerobic bacteria.
- Sign and Symptoms:
  - Same as septic arthritis
- Diagnosis
  - Same as septic arthritis
- Treatment:
  - Debridement
  - Include antibiotics that cover anaerobes and gram-negative bacteria
  - Piperacillin-tazobactam ± Vancomycin for MRSA
  - Nafcillin or Oxacillin + Rifampin for MSSA
  - Use Daptomycin for Vancomycin allergies and Ciprofloxacin for penicillin allergies

9.14.4 Diabetic foot infection

- Any foot infection in diabetic patients which ranges from superficial to deep infection such as osteomyelitis
- Common pathogens involved are:
  - *S. aureus*

  - Streptococcus sp.
  - *Enterococcus faecalis*
  - *P. aeruginosa*
  - *E. coli*
  - Anaerobes
- Sign and Symptoms:
  - Infection fails to heal.
  - Erythema, warmth, swelling, pain, and or purulent discharge.
  - Fever, chill, tachycardia, hypotension, or other sign of sepsis may be present.
- Diagnosis:
  - Clinical, such as the presence of ulceration >30 days or recurrent ulcer
  - Loss of sensation in the affected limb
  - Peripheral vascular disease
  - Peripheral neuropathy
  - Warmth, swollen, redness, and painful ulcer ± puss
  - Probe to bone, bone culture, or imaging investigation for possible osteomyelitis
- Treatment:
  - MSSA (Mild) → Cephalexin, Dicloxacillin, or fluroquinolone
  - MRSA (Mild) → SMZ-TMP or Doxycycline
  - MSSA (moderate to severe) → Cefoxitin, Ceftriaxone, Ampicillin-sulbactam, Carbapenem or piperacillin-tazobactam
  - MRSA (Moderate to severe) → Vancomycin, Daptomycin, or Linezolid

9.15 Fever of unknown origin (FUO)

- Fever greater than 101°F or 38.3°C for eight or more days of unknown cause after complete standard evaluation.
- Most common cause of FUO is infection
- Other causes are
  - Connective tissue disorder
  - Neoplastic disorder
  - Miscellaneous such as drug reaction, pulmonary embolism, sarcoidosis, inflammatory bowel disease
- Diagnosis:
  - Clinical
  - Complete blood count with differential
  - Erythrocyte sedimentation rate
  - Liver function test
  - Blood smears and culture
  - HIV testing
  - TB testing
  - Urinalysis

  - Chest X-ray and other imaging
  - Echocardiography
- Treatment
  - Based on the suspected cause

9.16 Sexually transmitted diseases

Can be classified into

- Bacterial
- Viral
- Parasitic

Risk factors:

- Unprotected sex
- Multiple sex partners
- Anonymous sex partners
- Sex under the influence of drugs or alcohol.

Prevention:

- Use condom
- Do not use risky sex activities
- Avoid multiple sex partners
- Avoid anal or oral sex

9.16.1 Bacterial sexually transmitted diseases

- Chancroid
- Gonorrhea
- Chlamydial, mycoplasmal, and ureaplasmal infections
- Granuloma inguinale
- Syphilis

9.16.1.1 Chancroid (Fig. 9.20)

- Caused by *H. ducreyi,* which is a gram-negative bacilli.
- Infection of genital skin or mucous membrane.
- Incubation time is 3–7 days.
- Infection starts with small, painful papules, which rapidly break down and become painful ulcer with irregular margins.
- *H. ducreyi* encode a cyto-lethal toxin which causes cell death of epithelial cells.
- Inguinal lymphadenopathy is common.

FIGURE 9.20 Chancroid. *Source: CDC (PHIL).*

- Highly contagious and prevalent in Asia, Africa, and Caribbean.
- Diagnosis:
  - Clinical evaluation See the image at www.images.Google.com
  - Culture or PCR
  - Serological testing of syphilis and HIV should also be done
- Differential Diagnosis:
  - Syphilis
  - Granuloma inguinale
  - Lymphogranuloma venereum
- Treatment:
  - Azithromycin 1 gm × one dose or
  - Ceftriaxone 250 mg IM as a single dose or
  - Erythromycin 500 mg TID × 7 days or
  - Ciprofloxacin 500 mg twice daily × 3 days
  - Sexual partner should also be treated if exposed during 10 days of development of symptoms.
- Complications:
  - Development of fistulous tract
  - Spread of infection deep, which result in the destruction of other tissue.

9.16.1.2 Gonorrhea

- Caused by N. gonorrhea, gram-negative diplococci.
- Responsible for infection of the urethra, cervix, rectum, pharynx, and conjunctivae.
- If untreated may cause disseminated gonorrhea, which infects multi organ system.
- Coinfection with *Chlamydia trachomatis* is about 25%–50%.
- Gonorrhea and Chlamydia are the most common STD worldwide.
- 50% of female patients are asymptomatic and responsible for spreading the disease.

- Risk factors:
  - Young age
  - History of STD
  - Multiple sex partners or partners with STI
  - Unprotected sex
  - Sexually abused children, sex workers, drug user
- Sign and Symptoms:
  - Depends on site of infection
  - Infection in Male:
    - Male urethritis
      - ➢ Incubation 2–14 days
      - ➢ Start with mild urethral discomfort followed by severe penile pain, dysuria, purulent discharge, urinary frequency, and inflamed urethral meatus.
    - Epididymitis:
      - ➢ Unilateral scrotal pain, swelling, and tenderness
- Infection in female
  - Cervical Infection
    - ➢ Incubation more than 10 days
    - ➢ Mild to severe symptoms
    - ➢ Dysuria and vaginal discharge
    - ➢ Painful sexual intercourse and or bleeding
    - ➢ Mucopurulent cervical discharge
    - ➢ Urethritis and pus
  - Pelvic Inflammatory disease:
    - ➢ Lower abdominal pain, dyspareunia, and tenderness on abdominal palpitation or cervix.
    - ➢ May result in salpingitis, pelvic peritonitis or abscess
- Nongenital infections
  - Conjunctival infection
    - ➢ Purulent eye discharge, eye pain, foreign body sensation, redness, and vision disturbance.
  - Neonatal infection
    - ➢ Meningitis, sepsis, conjunctivitis, arthritis, vaginitis, urethritis
  - Pharyngitis
    - ➢ Mostly asymptomatic but may cause sore throat.
  - Disseminated gonococcal Infection (DGI)
    - ➢ Fever, migratory polyarthritis, and pustular skin lesions.
- Complications:
  - Pelvic Inflammatory Disease, endometritis, salpingitis, ectopic pregnancy, infertility
  - Endocarditis

  - Meningitis, sepsis
  - Fitz-Hugh-Curtis Syndrome
  - Corneal ulceration and blindness
  - Preterm birth, perinatal mortality
- Diagnosis:
  - Gram staining and culture
  - Nucleic acid-based testing → preferred test
  - Antigen detection methods
  - Genetic prob methods
  - Rapid tests → rapid NAAT assay. It detects nucleic acid of N. *gonorrhoeae* and *C. trachomatis* and can process up to 96 specimens in less than 2 hours. Sensitivity is high, about 100%
- Screening
  - High risk individuals
  - Pregnant women during their first initial prenatal visit then again in third trimester if 24 years old or less or have risk factors.
- Treatment
  - First Choice: Ceftriaxone 250 mg IM × 1 + Azithromycin 1 gm PO × 1
  - Second Choice: Cefixime 400 mg PO × 1 + Azithromycin 1 gm PO × 1
  - Allergy to Azithromycin → use doxycycline 100 mg twice daily for 7 days.
  - Allergy to cephalosporin → Gemifloxacin 320 mg PO × 1 + Azithromycin 2 gm × 1
  - Gentamicin 240 mg IM + Azithromycin 2 gm × 1
  - Disseminated gonococcal infection → Ceftriaxone 1 gm IM followed by oral therapy for 7–10 days.
  - All sex partners who had sex with the patient within 60 days should be tested and treated presumptively.

9.16.1.3 Chlamydial infections

- Most common STD worldwide
- Most infected people remain asymptomatic and are the source of infection to others.
- Disease is caused by gram-negative, intracellular bacteria *C. trachomatis.*
- Incubation period 5–14 days.
- Risk factors:
  - Sex in Young age
  - Multiple sex partners
  - Unprotected sex
  - IV drug users, alcoholics, and sex trade workers
  - Douching
  - Previous history of STI
- Sign and symptoms: Depend on the site of infection:

  - Female:
    - Cervicitis: most common infected site results in nonspecific symptoms such as vaginal discharge, abnormal postcoital bleeding, abdominal pain, and painful intercourse.
    - Urethritis: Dysuria and pyuria, urgency and frequency.
    - Pelvic inflammatory disease (PID): Infection of cervicitis and urethritis, if not treated promptly, ascend to the upper reproductive tract and infect the uterus, fallopian tubes, and ovaries. Abdominal and pelvic pain and pain due to cervical motion, uterine or adnexal tenderness are common signs of PID. *N. gonorrhea* causes the same symptoms. However, *C. trachomatis* is associated with a higher rate of infertility, and ectopic pregnancy.
  - Male:
    - Urethritis: Most common cause of nongonococcal urethritis.
    - Watery or mucoid urethral discharge, dysuria, and frequent urination are the most common symptoms.
    - Epididymitis: Unilateral testicular pain and tenderness, swelling, and hydrocele.
    - Cause of chronic prostatitis.
  - Nongenital symptoms and complications:
    - Conjunctivitis, blindness, meningitis, pneumonia in newborns.
    - Pharyngitis
    - Rectal infection
    - Premature rupture of membrane, preterm birth, miscarriage, and still birth.
    - Infertility
    - Reactive arthritis
    - Fitz–Hugh–Curtis Syndrome.
- Diagnosis:
  - Nucleic Acid Amplification Test (NAAT): Preferred test
  - Rapid test: based on rapid NAAT test and provide the result in less than 90 min.
  - Culture: not routinely used
  - Serology test: use complement fixation titers
  - Antigen test: sensitivity is 80%–90%
  - Direct immunofluorescence assays or ELISA
  - Genetic probe test: sensitivity is about 80% and requires direct swab from the cervix or urethra.
- Screening:
  - High -risk individuals
  - History of SDI
  - Pregnant women at a first prenatal visit and repeat the screening later during gestation.
  - Gay men and women
  - Patient with HIV, hepatitis B and C.

- Treatment:
  - Azithromycin 1 gm × 1 or
  - Doxycycline 100 mg twice daily for 7 days or
  - Erythromycin 500 mg four times daily for 7 days or
  - Levofloxacin 500 mg daily × 7 days.

9.16.1.4 Mycoplasma hominis and ureaplasmas species

- These are small, gram-negative bacteria with no cell wall, therefore cannot be stained by gram stain. They are part of normal flora of genital tract of sexually active individuals.
- Not very common, these bacteria are associated with nongonococcal cervicitis, urethritis, PID, and other genital associated diseases.
- Their role in pregnancy related complications is not very clear.
- In neonate, they cause meningoencephalitis, bacteremia, pneumonia, although relatively uncommon and should be tested if initial laboratory tests are negative.
- Diagnosis:
  - Culture
  - Nucleic-acid-based tests
- Treatment, choice of antibiotics:
  - Doxycycline
  - Macrolides
  - Fluoroquinolone
  - Clindamycin

9.16.1.5 Lymphogranuloma venereum (LGV) (Fig. 9.21)

- Caused by *C. trachomatis* serotypes L1, L2, and L3.
- Common in tropical and subtropical areas but other areas such as Europe, North America, and Australia have reported sporadic outbreaks.
- Primarily infect men who have sex with men, but heterosexual persons can also be infected.

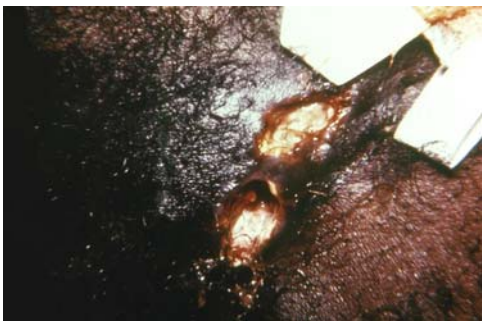

FIGURE 9.21 LGV. *Source CDC (PHIL).*

- About 75%–85% of infected persons are coinfected with HIV or have other SDIs.
- Sign and Symptoms: Three stages.
  - Primary stage:
    - Painless genital ulcer or papule develops after 3–12 days of exposure.
    - The lesion heals itself in few days and is usually unnoticed.
  - Secondary stage:
    - Occurs 2–6 weeks after the primary stage.
    - Patient develops painful unilateral or bilateral inguinal or lymphadenopathy called buboes.
    - The overlying skin is usually inflamed and forms characteristic groove sign.
    - The buboes rupture or discharge pus or blood and may form multiple sinus tracts.
    - Fever, malaise, backpain or pelvic pain are common, especially in women, due to vaginal and cervical lymph node retroperitoneal drainage.
    - Infection of the rectum's lymph node cause symptoms of proctocolitis with rectal discharge, pain, constipation, fever, and tenesmus.
    - Anorectal syndrome usually occurs when the transmission is via anal route.
    - Oral syndrome develops when infection is transmitted via oral route.
  - Third stage:
    - Lesion heal, but fibrosis, strictures, and sinus tract persist and result in late complications, such as anal fistulae, genital elephantiasis, frozen pelvis, and infertility. Severe case may result in esthiomene, which is a destruction of external genitalia usually seen in women.
    - Disease mimics chronic stage Crohn's disease.
- Diagnosis:
  - Clinical
  - Serology tests
  - Nucleic acid amplification test (NAAT)
- Treatment:
  - Doxycycline 100 mg twice daily × 21 days or
  - Erythromycin 500 mg four times daily × 21 days or
  - Azithromycin 1 gm every week × 3 weeks.

9.16.1.6 Granuloma Inguinale (Fig. 9.22)

- Rare infection caused by *Klebsiella granulomatis*
- Incubation period is 1–12 weeks
- Start with a painless nodule, which slowly enlarges, and develop into classic beefy-red appearance, raised, foul smelling lesion, which ulcerate, bleeds easily, and spreads to other are area of skin.
- Usually doesn't cause lymphadenopathy.
- Hematogenous spread to bone, liver, and other areas. May result in death if untreated.

FIGURE 9.22 Granuloma inguinale. *Source CDC (PHIL).*

Diagnosis

- Microscopic examination showing Donovan's bodies. Donovan bodies are basically bacteria in the cytoplasm of macrophages, which can be observed under the microscope after Giemsa or Wright staining.
- PCR
- Serological tests → not a diagnostic.

Treatment

- Doxycycline 100 mg twice daily × 3 weeks or more. or
- Erythromycin 500 mg four times daily for 3 weeks or more or
- Trimethoprim-sulfamethoxazole DS twice daily for 3 weeks or more.
- Partner should also be treated

9.16.1.7 Syphilis: see Section 4.5

9.16.2 Viral sexually transmitted infections

- Genital and anorectal warts
- Genital herpes
- Molluscum
- HIV infection

9.16.2.1 Anogenital warts (condylomata acuminata) (Fig. 9.23)

- Human papillomavirus (HPV) type 6 and 11 are the most common cause.
- HPV can categorize into high-risk types such as HPV 16, 18, 52, and 56, while types 6 and 11 are low-risk HPV. This category is based on the link to the development of cancer.

FIGURE 9.23 Condylomata acuminata. *Source CDC (PHIL).*

- Transmission from lesion to skin to skin contact
- Incubation period is one to 6 months.
- Risk factors:
  - Early age
  - Multiple sex partners
  - Unprotected sex
  - Cigarette smoking
  - Pregnancy
  - Immunocompromised
  - History of STIs or HIV
- Sign and symptoms:
  - Usually asymptomatic, but some patient feels burning, itching, or pain
  - Wart can be flat, popular, or pedunculated, soft pink or flesh colored growth.
  - Typically found on vulva, penis, groin, perineum, anal skin, and perianal area.
  - Wart grows in number after initial appearance and about 1/3 regresses within 4 months.
  - Infection persists even after the resolution of warts and warts may reoccur.
  - May result in anogenital, head and neck, cervical, vaginal, penile, and vulvar cancers if infected with high risk HPV.
  - Vaginal bleeding, painful intercourse if the pelvis is involved.
- Diagnosis:
  - Clinical
  - Serological tests
  - Pap smears → HPA DNA test
  - Biopsy

- Treatment:
  - There is no cure for HPV. Most cases resolve itself in 1–2 years. But the virus remains dormant inside the host body and may reoccur.
  - Mechanical removal → Cryotherapy, surgical removal, excision, curettage, laser, or electrosurgery.
  - Topical treatment → Imiquimod 3.75%–5% cream, Podofilox 0.5% solution, Sinecatechins 15% ointment.

9.16.2.2 Genital herpes (Fig. 9.24)

- Common sexually transmitted disease caused by herpes simplex virus (HSV).
- Most of the genital herpes is caused by HSV type II, while the infection in mouth is mostly associated with HSV type I, but incidence of genital herpes caused by HSV type I are increasing.
- The infection is transferred by close contact with skin, mucous membrane, or genital or oral secretions.
- The virus replicates in epithelial cells and migrate to sensory ganglia where it remains dormant and periodically reactivate and causing the lesions.
- Pregnant women can transmit the virus to fetus transplacentally (rare) or during delivery via contact with vaginal secretions.
- Risk factors:
  - Unprotected sex
  - Multiple sex partners
  - Oral-genital sex
  - Female sex
  - Use of hormonal contraceptive
  - History of SDIs and HIV
- Sign and symptoms:
  - Primary infection: sign and symptoms of primary infection vary from asymptomatic to severe painful genital ulcers, dysuria, fever, headache, local lymphadenopathy.

FIGURE 9.24 Genital herpes. *Source CDC (PHIL).*

  - Skin lesion is group vesicles with erythema, pustules, and ulcers.
  - Common site of lesions are penis glans, prepuce, and penile shaft for men
  - For female usually on labia, clitoris, perineum, vagina, and cervix
  - Primary lesions have more severe symptoms than recurrence lesions.
  - Recurrent Infection: less severe than primary infection, and shorter duration
- Complications:
  - Meningitis
  - Sacral radiculitis
  - Proctitis
  - Urinary retention
  - Pneumonia
  - Increased risk of HIV infection
- Viral shedding: Intermittent viral shedding occurs even with no lesions. This shedding is more common in primary infection caused by HSV type II.
- Diagnosis:
  - Clinical
  - Culture
  - PCR
  - Serological tests
- Treatment:
  - Acyclovir 400 mg orally three times daily for 7–10 days
  - Valacyclovir 1 gm orally q12h for 7–10 days
  - Famciclovir 250 mg orally three times daily for 7–10 days

9.16.2.3 Molluscum contagiosum (Fig. 9.25)

- Cluster of pink, domed shaped, central umbilicated papules arises on mouth, trunk, genital area, and any other part of body except sole and palm.
- Papules may be pruritic.
- Caused by Molluscum contagiosum virus which belong to poxvirus family and is double stranded DNA virus

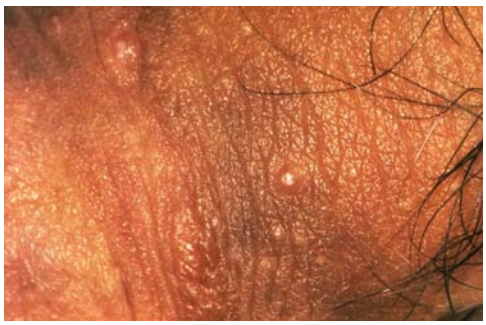

FIGURE 9.25 Molluscom contagiosum. *Source: CDC (PHIL).*

- Transmission
  - Incubation period is 2–6 weeks
  - Close contact (skin to skin contact).
  - Fomites.
  - Contact sports.
  - Sexual contact. See the image at www.images.google.com
  - Swimming pool.
- Risk factors:
  - Children
  - Close contacts with infected person
  - Immunocompromised
  - Atopic dermatitis
- Diagnosis:
  - Clinical
  - Skin biopsy → shows inclusion bodies.
- Treatment:
  - Most lesions regress in 1–2 years
  - Treatment is needed for cosmetic reason which includes:
    - Physical removal such as curettage, cryosurgery, laser surgery.
    - Use of topical irritant → trichloroacetic acid, cantharidin, tazarotene.

9.16.2.4 HIV infection: see Section 6.13

9.16.3 Parasitic sexually transmitted infections

- Trichomoniasis
- Scabies
- Pediculosis pubis

9.16.3.1 Trichomoniasis: also see Section 6.2.2.8

- Most common nonviral STI worldwide.
- Caused by protozoan *T. vaginalis* (Fig. 9.26).
- More common in women than in men.
- Men are mostly asymptomatic.
- Risk factors:
  - Multiple sex partners
  - Unprotected sex
  - History of STIs
  - Young age
  - Low socioeconomic status
  - Drug user

FIGURE 9.26 Trichomonias. *Source: CDC (PHIL).*

- Incarceration

- Sign and symptoms:

  Female.
  - Purulent, malodorous (fishy), yellow-green frothy discharge with vaginal burning, pruritis, dysuria, frequency, and lower abdominal pain.
  - Physical exam shows inflamed vulva, and perineum. Vaginal wall or cervix may have punctate hemorrhages (strawberry cervix) only in 2% women.
  - About 85% infected women are asymptomatic
  - Pregnant women: infection in pregnant women may result:
    - Premature rupture of membrane
    - Preterm delivery
    - Low birth weight
    - Newborn may get infected during delivery → fever, respiratory problem, urinary tract infection, nasal discharge, vaginal discharge (girls).

  Male.
  - Infection in male is mostly asymptomatic and they are the silent carrier of the infection
  - Patient may develop sign of urethritis with mucopurulent urethral discharge, ± dysuria, pruritis or burning.
  - Untreated infection may result in prostatitis, balanoposthitis, epididymitis, infertility, and prostate cancer.

- Diagnosis:
  - Microscopic exam of the secretion (wet mount). Visualize trichomonads. Sensitivity decrease with time as organism is motile for only 10–20 min after collection.
  - PH > 4.5 not a diagnostic
  - Nucleic acid amplification tests (NAAT)
  - Immunochromographic flow dipstick test → rapid test
  - Culture of urethral swab or urine (men)

- Treatment:
  - Metronidazole 2 gm × 1 for patient and partner
  - Tinidazole 2 gm × 1 for patient and partner

9.16.4 Vaginitis: clinical differences (Table 9.20)

Table 9.20 Causes and symptoms of vaginitis.

Subjective	Normal	Candidiasis	Bacterial vaginosis	Trichomoniasis
Etiology	Normal flora comprises of mostly lactobacillus species	*Candida albicans, C. krusei, C. glabrata*	*Gardnerella vaginalis, mycoplasma hominis,* anaerobic bacteria,	*Trichomonas vaginalis* (STD)
Discharge	White or transparent thin or thick, odorless discharge. Usually 1–4 mL in 2 h.	White, thick, odorless	White or gray fishy odor	Green-yellowish frothy, malodorous
Pruritis	No	Yes	Mild	Mild
Pain	No	Dyspareunia, dysuria	No	Dyspareunia, dysuria, burning, postcoital bleeding
Inflammation	No	Vulvar erythema and vaginal inflammation	No	Vulvovaginal erythema Strawberry cervix
PH	4.0–4.5	4.0–4.5	>4.5	5.0–6.0
Whiff test/Amine test. (Amine odor by mixing 10% potassium hydroxide with the vaginal discharge	Negative	Negative	Positive, sensitivity 67%, specificity 93%	Positive, sensitivity 67%, specificity 65%
Microscopic exam Saline/10% potassium hydroxide	Few neutrophil, several vaginal epithelial cells. Ratio is < 1 (PMN:VEC)	PNM:VEG<1, pseudo-hyphae, budding filaments, sensitivity 61% specificity 77%	PNM:VEG<1, clue cells, coccobacilli, absent lactobacilli. Sensitivity 53%–90%, specificity 40%–100%	Lot of PNM cells, motile trichomonads. Sensitivity 50% –70%, specificity 100%
Treatment	None	Intravaginal antifungal, Oral fluconazole	Metronidazole oral	Metronidazole/ tinidazole oral

9.17 Prion

Prions are protein molecules found in the cell membrane of neurons. Prion proteins (PrP^C) are mostly folded in alpha-helices and coded by PrpNP gene on chromosome 20. For reasons mostly unknown these proteins get misfolded and become highly resistant

to enzymatic break down. This results in accumulation of prion proteins (PrP^{Sc}) in the neurons and form plaques. It also triggers apoptosis of neurons, formation of cysts, degeneration of cerebral cortex, cerebellum, and spongy appearance called "Spongiform Encephalitis."

9.17.1 Type of prions disease

- Creutzfeldt- Jakob disease (CJD): Rapidly progressive disease with dementia. It is of four types
  - Sporadic → Most common. Idiopathic
  - Familial (fCJD) → mutation @ 200th codon and cause change of glutamic acid to lysine
  - Variant (vCJD) → caused by eating infected cow meat (mad cow disease)
  - Iatrogenic (iCJD) → Usually caused by using contaminated medical equipment for the procedures
- Kuru: Tribe in New Guinea who practiced ritual cannibalism infected with the disease. Acquired form
- Fatal Insomnia: Inherited or sporadic mutation in the prion gene on chromosome 20, codon 178. Aspartic acid is changed to asparagine which result in misfold proteins which is deposited in thalamus rather in cerebral cortex and cerebellum.
- Gerstmann-Straussler-Scheinker Syndrome: Inherited form
- Sign and Symptoms:
  - Sign and symptoms may not appear for decades
  - Early symptoms: Ataxia, memory loss, and behavioral changes
  - Late symptoms: Muscles weakness, abnormal jerky muscles movement, dementia, unable to perform normal functions, insomnia, hallucination, and death
- Diagnosis:
  - MRI → Presence of lesions
  - CSF → Elevated protein of 14-3-3 (sign of neuronal destruction)
  - Brain biopsy
- Treatment:
  - No treatment available
  - Supportive

9.18 Quick reference of common infections, pathogens, and treatments

Infection	Pathogen	Treatment first choice	Second choice
Meningitis/Encephalitis			
Viral	HSV, VZV, enterovirus, West nile virus, parechoviruses	Acyclovir supportive for West nile virus	Valacyclovir
Bacterial age < 6week	Group B streptococcus (strep. agalactiae), *E. coli*, S. pneumoniae, listeria species.	1) Cefotaxime[1] + ampicillin + gentamicin ± vancomycin if MRSA is suspected	1) Ceftazidime + ampicillin 2) Ampicillin + gentamicin
Children and adults Community acquired	S. Pneumoniae, N. meningitidis, H. influenzae, listeria.	1) Ceftriaxone[2] + vancomycin + ampicillin ± dexamethasone.	1) Meropenem + vancomycin ± dexamethasone. 2) Chloramphenicol + TMP-SMX + Vancomycin → severe penicillin allergy.
Hospital acquired	S.Pneumoniae, S.aureus, and other staphS species. P.aeruginosa, gram-negative bacilli.	1) Cefepime + vancomycin * add dexamethasone.	1) Meropenem + vancomycin + gentamicin ± dexamethasone. 2) Vancomycin + aztreonam + TMP-SMX → allergy to penicillin 3) Vancomycin + ciprofloxacin + TMP-SMX → allergy to penicillin
Fungus	Candida species	1) Amphotericin B ± flucytosine	1) Fluconazole → allergy to amphotericin or step-down therapy 2) Voriconazole
	Blastomyces	1) Amphotericin B × 4–6 weeks, then fluconazole or voriconazole × 12 months.	1) Itraconazole + amphotericin B
	Histoplasma species	1) Amphotericin B × 4–6 weeks then itraconazole × 12 months.	1) Fluconazole 2) Voriconazole 3) Posconazole
	Coccidioides immitis.	1) Fluconazole	1) Itraconazole 2) Voriconazole 3) Amphotericin B
	Cryptococcus species	1) Amphotericin B + flucytosine followed by fluconazole.	1) Fluconazole + flucytosine 2) Fluconazole

[1] and [2] = Can be replaced by Ceftriaxone, Ceftazidime, or Cefepime.

Tuberculosis	*M. tuberculosis*	1) Rifampin + Isoniazid + Pyrazinamide + Ethambutol × 2 months, then rifampin + isoniazid × 6–7 months ± dexamethasone × 3–4 weeks.	See Section 4.6
Lyme disease	B. Burgdorferi	1) Ceftriaxone 2) Doxycycline	1) Penicillin G 2) Cefatoxime
Syphilis	T. pallidum	1) Penicillin G	1) Procaine penicillin G + probenecid 2) Ceftriaxone
Amebic	Acanthamoeba	1) Pentamidine + fluconazole + miltefosine ± metronidazole.	None
	Naegleria fowleri	1) Amphotericin B + rifampin + fluconazole + miltefosine + azithromycin.	None
	Balamuthia mandrillaris	1) Albendazole + fluconazole + miltefosine.	None
Brain abscess			
Bacterial	Streptococcus species Bacteroide Enterobacteriaceae *Staphylococcus aureus*.	1) Ceftriaxone* + metronidazole ± vancomycin if *S. aureus* suspected. * can be replaced by cefotaxime or cefepime	1) Penicillin G + metronidazole 2) Meropenem Add vancomycin to above regime if *S. aureus* is suspected.
	Nocardia	1) Imipenem-cilastatin + TMP-SMX ± amikacin if multiorgan involved.	1) Linezolid + meropenem
Parasitic	T. gondii	1) Pyrimethamine + sulfadiazine + folic acid 2) TMP-SMX → prophylaxis	1) Pyrimethamine + clindamycin or atovaquone + folic acid. 2) Pyrimethamine + azithromycin.
Fungal	Mucor, rhizopus, phaeophyphomycosis	1) Amphotericin B	1) Itraconazole
Viral	HSV type 1 and 2, VZV, HHV type 6	1) Acyclovir	2) Valacyclovir
Infection	Pathogen	First choice	Second choice
Eyes			
Conjunctivitis			
Viral	Adenovirus, enterovirus, HSV.	1) Supportive 2) HSV → acyclovir IV	1) None.
Bacterial	*S. aureus* *S. pneumoniae* *H. influenzae* *M. catarrhalis*	1) Moxifloxacin ophthalmic drops. 2) Ciprofloxacin opth. Drops 3) Polymyxin B–Trimethoprim opth.	1) Azithromycin ophthalmic drops.

(*continued on next page*)

	N. gonorrhea *C. trachomatis*	1) Ceftriaxone IV/IM + azithromycin	1) Azithromycin PO 2) Doxycycline PO
Stye	*S, aureus*	1) Warm compress 2) Cephalexin Po	1) Dicloxacillin 2) SMZ-TMP PO
Dacryocystitis	*Strep. pneumoniae* *Staph. aureus* *H. influenzae* *Strep. pyogenes*	1) Cephalexin PO 2) Amoxicillin-clavulanate Po 3) TMP-SMX PO	1) Vancomycin if MRSA 2) Nafcillin IV 3) Cefazolin IV
Uveitis			
Viral	HSV, VZV, CMV	1) Acyclovir IV or PO 2) Ganciclovir for CMV	1) Valacyclovir 2) Valganciclovir for CMV 3) Foscarnet for CMV
Spirochete	*T. pallidum* T. gondii	1) Penicillin G IM × 1 dose 2) Pyrimethamine + sulfadiazine For T. gondii.	1) Ceftriaxone 2) Pyrimethamine + clindamycin for T.gondii
Keratitis			
Viral	HS V, VZV, adenovirus	1) Trifluridine ophthalmic for HSV. 2) Famciclovir or valacyclovir for VZV. 3) Adenovirus→ none	None
Bacterial	Staph. aureus Coagulase -ve staph Strep. pyogenes *P. aeruginosa* Enterobacteriacae	1) Ciprofloxacin ophthalmic drops. 2) Levofloxacin ophthalmic drops.	1) Tobramycin ophthalmic 2) Tobramycin ophthalmic
Fungal	Aspergillus Candida Fusaium	1) Natamycin optic drops × 14–21 days.	1) Amphotericin optic drops 2) Amphotericin IV 3) Itraconazole PO
Protozoal	Acanthameba	1) Biguanide chlorhexidine optic + propamidine or hexamidine.	1) None
Cavernous sinus thrombosis	*S. aureus* Streptococcus species H. Influenzae Anaerobes	1) Nafcillin or oxacillin + ceftriaxone. 2) Vancomycin + ceftriaxone if MRSA is suspected. 3) Add metronidazole if anaerobes are suspected	1) Daptomycin or linezolid + ceftriaxone. Add metronidazole if anaerobes are suspected. 2) Cefepime + metronidazole
Orbital cellulitis	S. Pneumoniae Staph. aureus Strep. pyogenes	1) Vancomycin + ceftriaxone + metronidazole. 2) Piperacillin-tazobactam 3) Ampicillin-sulbactam	2) Vancomycin + moxifloxacin

Mouth and respiratory tract			
Herpes labialis (cold sore)	HSV type 1and 2	1) Valacyclovir PO 2) Acyclovir PO 3) Famciclovir PO	1) Penciclovir 1% topical cream 2) Acyclovir topical cream ± fluocinonide cream.
Dental Tooth and odontogenic infection, Ludwig's angina	Viridian group Oral anaerobes Strep. pyogenes Staph. aureus Gram -ve bacteria	1) Penicillin G + metronidazole 2) Piperacillin-tazobactam * Add vancomycin if Staphylococcus sp. is suspected	1) Amoxicillin-clavulanate 2) Meropenem 3) Clindamycin if penicillin allergy
Periodontitis, necrotizing gingivitis, Vincent's angina	Mixed oral anaerobes	1) Penicillin G + metronidazole	1) Clindamycin
Oropharyngeal candidiasis	Candida albicans	1) Clotrimazole troches 2) Nystatin suspension 3) Fluconazole PO	1) Itraconazole 2) Voriconazole 3) Posaconazole 4) Caspofungin or micafungin IV.
Parotitis	Staph. aureus Strep. pyogenes Mixed anaerobes Gram -ve bacilli	1) Nafcillin or oxacillin + metronidazole. 2) Vancomycin + metronidazole if MRSA is suspected	1) Clindamycin 2) Linezolid + meropenem if immunosuppressive.
Mumps Pharyngitis/Tonsilitis	Paramyxovirus	Supportive, vaccine	None
Bacterial	Streptococcus species C. diphtheria N. gonorrhae *C. trachomatis*	1) Penicillin VK 2) Amoxicillin-clavulanate 3) Clindamycin	1) Cephalosporin 2) Ceftriaxone + azithromycin if STD related. 3) Azithromycin
Viral	EBV, HIV, HSV, influenza virus	Supportive, HIV related use HIV antiviral drugs	None
Site of infection	**Pathogens**	**First choice**	**Second choice**
Epiglottitis			
Bacterial	Strep. pyogenes Strep. pneumoniae Staph. aureus H. Influenzae	1) Ceftriaxone or cefotaxime + vancomycin 2) Vaccine for H. influenzae	1) Levofloxacin + clindamycin
Viral	Influenza virus Parainfluenza virus HSV, VZV, EBV	1) Supportive 2) Vaccine	1) None

(*continued on next page*)

Croup	Parainfluenza virus RSV, adenovirus, Influenza virus	1) Supportive 2) Epinephrine 3) Dexamethasone	None
Parapharyngeal abscess/infection	Anaerobes *S. aureus* Streptococcus species	1) Ceftriaxone + metronidazole 2) Levofloxacin + clindamycin	1) Piperacillin-tazobactam 2) Cefepime + metronidazole
Common cold	Rhinovirus Coronavirus Parainfluenza virus	1) Supportive	1) None
Influenza	Influenza virus A&B Avian influenza H5N1 and H7N9.	1) Supportive 2) Oseltamivir PO	1) Zanamivir inhalation sol. 2) Baloxavir PO 3) Laninamivir inhalation sol
Pertussis (whooping cough).	Bordetella pertussis	1) Supportive 2) Azithromycin 3) Erythromycin * Shorten the disease course if given in catarrhal stage	1) Clarithromycin 2) TMP-SMZ
Sinusitis			
Viral	Influenza virus Parainfluenza virus Rhinovirus	1) Supportive	1) Supportive
Bacterial	Strep. pneumoniae H. Influenzae M. catarrhalis Staph. aureus Anaerobes	1) Amoxicillin-clavulanate 2) Amoxicillin	1) 2nd or 3rd generation cephalosporin 2) Levofloxacin 3) Doxycycline 4) Clindamycin
Fungal	Aspergillus, mucor	Voriconazole ± caspofungin or micafungin.	None
Infection site	**Pathogens**	**First choice**	**Second choice**
Bronchitis			
Viral	Rhinovirus, parainfluenza virus, influenza virus, RSV, coronavirus	Supportive	Supportive
Bacterial	M. Pneumoniae Chlamydia pneumoniae Bordetella pertussis	1) Azithromycin 2) Clarithromycin 3) Ceftriaxone	1) Levofloxacin* 2) Cefepime* 3) Piperacillin-tazobactam* * Suspected pseudomonas
Bronchiolitis	RSV, rhinovirus, influenza virus, parainfluenza virus, Adenovirus, coronavirus	Supportive	Supportive

Pneumonia			
Viral	RSV, adenovirus, influenza virus, coronavirus (SARS-cov-2), CMV in organ transplants	1) Supportive, see Section 6.3.5 for COVID-19. 2) Ganciclovir × 14 days for CMV	1) Foscarnet for CMV 2) Cidofovir for CMV
Bacterial	Strep. pneumoniae M. catarrhalis H. Influenzae	Outpatient: 1) Amoxicillin 2) Amoxicillin-clavulanate	
Community acquired	Staph. aureus M. pneumoniae Legionella	Inpatient 1) Ceftriaxone + azithromycin	1) Levofloxacin 2) Azithromycin 3) Doxycycline
Hospital acquired	Same as above + *P. aeruginosa*, staph aureus including MRSA, gram -ve Bacilli.	No risk factors 1) Ceftriaxone With risk factors 1) Piperacillin-tazobactam + vancomycin or linezolid	1) Levofloxacin 1) Levofloxacin 1) Levofloxacin + vancomycin 2) Meropenem + vancomycin 3) Aztreonam + vancomycin * vancomycin can be substituted with linezolid.
Aspiration PNA	Oral anaerobes Gram-positive cocci Enterics Gram-negative bacteria	1) Levofloxacin + metronidazole 2) Ceftriaxone + metronidazole	1) Amoxicillin-clavulanate 2) Clindamycin ± levofloxacin 3) Piperacillin-tazobactam 4) Carbapenem ± clindamycin or metronidazole
Alcoholic PNA	Same pathogens as in hospital acquired PNA + Klebsiella, and oral anaerobes	Same as aspiration pneumonia	Same as in aspiration pneumonia.
Immunocompromised patient.	All pathogens responsible for hospital acquired PNA + P. jiroveci, nocardia Fungi, CMV, HSV	1) Same as in hospital acquired pneumonia.	Same as hospital acquired pneumonia
Fungal PNA	Coccidioidomycosis Histoplasma species.	1) Fluconazole 2) Itracanazole	1) Amphotericin B

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Ear infection			
Acute otitis media	Viruses (70%) Strep. pneumoniae H, influenzae Moraxella catarrhalis	1) Amoxicillin (high dose) 2) Amoxicillin-clavulanate 3) Ceftriaxone	1) Cefidinir 2) Cefprozil 3) Levofloxacin $) moxifloxacil 6) Azithromycin (not very effective)
Mastoiditis (acute)	Strep. pneumoniae Strep. pyogenes Staph. aureus *P. aeruginosa*	1) Piperacillin-tazobactam + vancomycin 2) Ceftazidime + vancomycin	1) Aztreonam + vancomycin for beta-lactam allergy 2) Ciprofloxacin or levofloxacin + vancomycin
Chronic	Mixed bacteria	1) Ciprofloxacin	1) Levofloxacin
Otitis externa malignant	*P. aeruginosa* Staph. aureus Aspergillus fungus	1) Ciprofloxacin 2) Piperacillin-tazobactam 3) Meropenem	1) Cefepime 2) Ceftazidime 3) Levofloxacin
Gastro-intestinal tract			
Diarrhea			
Viral	Rotavirus, norovirus, astrovirus	Supportive, fluid replacement and electrolytes	None
Exotoxin mediated	Staph. aureus, B. cercus, *C. perfringens*	Self-limiting, IV fluids and electrolytes.	None
History of antibiotics use	*C. difficile*	1) Vancomycin PO 2) Fidaxomycin PO	See section 3.3.1.4
Traveler's diarrhea	*E. coli* (enterotoxigenic ETEC), shigella species, salmonella species Campylobacter species	1) Azithromycin PO 2) Ceftriaxone → pediatrics	1) Ciprofloxacin 2) Levofloxacin 3) Rifaximin
Bloody diarrhea without fever	*E. coli* (shiga like toxin-STEC).	Hydration with electrolytes Use of antibiotics ↑the chances of hemolytic uremic syndrome.	None
Bloody diarrhea with fever	Salmonella sp. Shigella sp. C. jejoni, Vibrio sp. Yersinia sp.	1) Ciprofloxacin 2) Azithromycin	1) Doxycycline + ceftriaxone for vibrio 2) TMP-SMX → Yersinia
Subacute	Giardia, cryptosporidium, Entamoeba histolytica	1) Metronidazole 2) Tinidazole	1) Paromomycin or iodoquinol for intestinal cysts. 2) Nitazoxanide for cryptosporidium.
Appendicitis	Enterobacteriaceae Bacteroides Enterococcus species	**No-perforated** 1) Ceftriaxone + metronidazole **Perforated** 1) Piperacillin-tazobactam 2) Meropenem 3) Ciprofloxacin + metronidazole	1) Ertapenem 1) Doripenem

Actinomycosis	Actinomyces species	1) Penicillin G 2) Amoxicillin	1) Doxycycline 2) Clindamycin 3) Ceftriaxone
Diverticulitis	Enterobacteriaceae Bacteroides Enterococcus P, aeruginosa	Mild infection 1) Amoxicillin-clavulanate Mild to moderate 1) Piperacillin-tazobactam 2) Cefepime + metronidazole **Severe infection** 1) Ampicillin + ciprofloxacin + metronidazole	1) Moxifloxacin 1) Ciprofloxacin + metronidazole 1) Ceftazidime − avibactam + metronidazole. 3) Aztreonam + metronidazole
Enterocolitis	Mixed infection with gram + ve and gram -ve bacteria including anaerobes.	1) Cefepime + metronidazole 2) Piperacillin-tazobactam	1) Meropenem
Esophagitis			
Viral	CMV	1) Ganciclovir	1) Foscarnet 2) Cidofovir
Fungal (AIDS)	Candida albicans	1) Fluconazole PO	1) Micafungin or caspofungin. 2) Amphotericin B IV 3) Itraconazole
Gallbladder Cholangitis, biliary sepsis, and obstructuction	Enterobacteriaceae Enterococci Bacteroides Clostridium species	1) Piperacillin-tazobactam 2) Meropenem	1) Ciprofloxacin + metronidazole 2) Ceftriaxone + metronidazole
Liver			
Viral (see Section 6.7) Liver abscess	See Section 6.7 Enterobacteriaceae Bacteroides Enterococcus Entamoaba histolytica Echinococcus	See Section 6.7 1) Ceftriaxone + metronidazole 2) Piperacillin-tazobactam + metronidazole	See Section 6.7 1) Ciprofloxacin + metronidazole 2) Ertapenem + metronidazole

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Pancreatic abscess	Enterobacteriaceae Enterococcus sp. Anaerobes Staphylococcus species	1) Meropenem 2) Imipenem-cilastatin 3) Moxifloxacin	1) Ciprofloxacin + metronidazole 2) Ciprofloxacin + metronidazole
Spontaneous bacterial peritonitis	Enterobacteriaceae Streptococcus species Staphylococcus species Enterococcus species	1) cefoxitin 2) Ceftriaxone 3) Ciprofloxacin	1) Ertapenem 2) Piperacillin-tazobactam
Bowel perforation	Same as above + anaerobes	1) Piperacillin-tazobactam 2) Meropenem 3) Ertapenem	1) Ciprofloxacin + metronidazole
Whipple disease	*Tropheryma whipplei*	1) Doxycycline + hydroxychloroquine	1) Ceftriaxone followed by TMP-SMZ

Sepsis

Treatment is based on the source of infection if known

Source of infection

PNA (community)	Strep. Pneumonia Staph. aureus M. catarrhalis Legionella Gram -ve bacilli	1) Ceftriaxone + azithromycin ± vancomycin if MRSA is suspected.	1) Levofloxacin or moxifloxacin ± vancomycin if MRSA is suspected.
PNA (nosocomial)	Same as above + *P. aeruginosa*, enterics	1) Piperacillin-tazobactam or cefepime + vancomycin 2) Aztreonam + vancomycin for penicillin allergy.	1) Piperacillin-tazobactam + levofloxacin + vancomycin for double anti-pseudomonas coverage. 2) Meropenem + vancomycin for unstable patient. 3) Replace vancomycin with linezolid if VRE suspected.
Skin	Staph. aureus Strep. pyogenes Strep. agalactiae Pseudomonas	1) Piperacillin-tazobactam or cefepime + vancomycin. Add clindamycin if nectrotizing soft-tissue infection is suspected.	1) Levofloxacin or ciprofloxacin + vancomycin 2) Aztreonam + vancomycin for penicillin allergy
Biliary	Enterobacteriaceae Enterococci Bacteroides	1) Piperacillin-tazobactam 2) Ceftriaxone + metronidazole	1) Ciprofloxacin or levofloxacin + metronidazole

Unknown	No ESBL suspected	1) Piperacillin-tazobactam + vancomycin.	Cefepime + vancomycin
	ESBL suspected	1) Meropenem + Vancomycin	1) Ertapenem + vancomycin
	Carbapenemases producing bacteria	1) Ceftazidime-avibactam + vancomycin	Meropenem-vaborbactam + vancomycin
Neonatal sepsis	Strep. agalactiae *E. coli* Klebsiella species Enterobacter species Enterococcus species Listeria H. Influenzae	1) Cefotaxime + ampicillin ± gentamicin. Add vancomycin if MRSA is suspected. * clindamycin for penicillin allergy	1) Ampicillin + ceftriaxone ± gentamicin. Add vancomycin if MRSA is suspected.
Toxic shock syndrome	Clostridium sordelli	1) Penicillin G + clindamycin	1) Carbapenem
	Staphylococcus species	2) Nafcillin or oxacillin + clindamycin. Add vancomycin if MRSA	2) Chloramphenicol 3) Cefazolin + clindamycin
	Streptococcus	1) Penicillin G + clindamycin 2) Vancomycin + clindamycin if penicillin allergy.	Ceftriaxone + clindamycin
Skin/Soft tissue infection			
Viral			
German measles	Rubella virus	Supportive, No vaccine	None
Measles	Rubeola virus	Supportive, MMR vaccine	None
HSV lesions	HSV	1) Valacyclovir 2) Acyclovir	1) Famciclovir
Roseola infantum	HHV types 6 and 7	Supportive, no vaccine	None
Shingles	Herpes zoster virus	1) Valacyclovir PO 2) Acyclovir PO	Acyclovir IV for severe infection.
Warts	Human papillomavirus	1) Cryotherapy, electocauterization, laser, surgical 2) Podofilox solution 3) Imiquimod cream	1) Sinecatechins 2) Vaccine
Bacterial			
Animal bites			
Dogs	Pasteurella canis Staph. aureus Bacteroides Fusobacterium	1) Amoxicillin-clavulanate 2) Clindamycin + TMP-SMZ *Rabies immunoglobulin + vaccine for dog bites that is not immunized	1) Ciprofloxacin or levofloxacin + clindamycin.

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Cats	Pasteurella multocida Staph. aureus Bartonella henselae Anaerobes (oral)	1) Amoxicillin-clavulanate 2) Doxycycline	1) Ceftaroline
Human	Streptococcus species Staph aureus Eikenella corrodens Oral anaerobes	1) Amoxicillin-clavulanate 2) Piperacillin-tazobactam 3) Add vancomycin or daptomycin if MRSA is suspected	1) Clindamycin + ciprofloxacin or levofloxacin
Bat, racoon, stunk	Streptococcus species Staphylococcus species	1) Amoxicillin-clavulanate *Rabies immunoglobulin + vaccine for dog bites that is not immunized	2) Doxycycline
Monkey, or other primates bite	Herpes simiae virus	1) Valacyclovir (post exposure prophylaxis 2) Acyclovir (treatment)	1) Ganciclovir (treatment if + CNS symptoms).
	Bacterial Haemophilus species Oral anaerobes Streptococcus species Wolinella species Compylobacter species Eikenella corrodens	1) Amoxicillin-Clauvlanate 2) Ampicillin-sulbactam 3) Piperacillin-tazobactam *Add vancomycin if MRSA is suspected *Tdap vaccine if > 10 years from the last dose.	1) Meropenem 2) Clindamycin + ciprofloxacin or levofloxacin.
Snake bite	Enterobacteriaceae Pseudomonas species Staph. epidermidis Clostridium species	1) Antivenom 2) Amoxicillin-clavulanate + ciprofloxacin 3) Piperacillin-tazobactam	* May consider tetanus immunoglobulin and vaccine
Burns	Strep. pyogenes Enterobacteriaceae Staph. aureus Staph. epidermidis Enterococcus species Pseudomonas species E.Coli Candida species	1) Vancomycin + Meropenem *Vancomycin can be switched with daptomycin. Fluconazole	1) Vancomycin + cefepime + fluconazole 2) Aztreonam + vancomycin if allergy to beta-lactam.
Cellulitis/Erysipelas	Strep. pyogenes Staph. aureus	1) Ceftriaxone 2) Cephalexin * add vancomycin or linezolid if MRSA is suspected	1) Azithromycin 2) SMZ-TMP * add vancomycin or linezolid if MRSA is suspected.

Folliculitis/Carbuncle /Furuncle.	Staph. aureus *P. aeruginosa*	1) Clindamycin topical 2) Erythromycin topical 3) Mupirocin * Use vancomycin or linezolid if MRSA is suspected	1) TMP-SMX 2) Doxycycline 3) Erythromycin
Ecthyma/Impetigo	Staph. aureus Strep. Pyogenes	1) Mupirocin topical 2) Bacitracin topical	1) Cephalexin PO 2) Dicloxacillin PO 3) Clindamycin PO 4) TMP-SMX PO
Necrotizing soft tissue infection	Polymicrobial aerobic and anaerobic organisms	1) Piperacillin-tazobactam + vancomycin or linezolid. 2) Ceftriaxone + metronidazole ± vancomycin	Ciprofloxacin or levofloxacin + metronidazole ± vancomycin
Staphylococcal scalded skin syndrome (toxin)	Staph. aureus	1) Nafcillin 2) Vancomycin if MRSA	1) Linezolid 2) Daptomycin
Urinary tract infection (UTI)			
Asymptomatic bacteriuria	Gram - ve bacteria	No treatment	Amoxicillin or cephalosporin for pregnant women
Uncomplicated UTI	Enterobacteriaceae S. Saprophyticus Enterococcus	1) TMP-SMX 2) Nitrofurantoin 3) Fosfomycin	1) Ciprofloxacin 2) Levofloxacin 3) Cephalosporin
Complicated UTI	Enterobacteriaceae *P. aeruginosa* Enterococcus	1) Ciprofloxacin 2) Levofloxacin	1) Piperacillin-tazobactam 2) Cefepime
Cystitis	*E. coli* *P. mirabilis* S. Saprophyticus *K. pneumoniae*	1) TMP-SMX 2) Nitrofurantoin 3) Fosfomycin	1) Ciprofloxacin 2) Levofloxacin 3) Amoxicillin-clavulanate 4) Cephalaxin
Pyelonephritis	Enterobacteriaceae Enterococcus *P. aeruginosa*	1) Ciprofloxacin 2) Levofloxacin 3) Ceftriaxone if no risk of pseudomonas.	4) Ertapenem 5) Meropenem 6) Gentamicin
Prostatitis	*E. coli* *P. mirabilis* Pseudomonas species	1) Ciprofloxacin 2) Levofloxacin 3) Ampicillin + gentamicin	1) TMP-SMX 2) Azithromycin 3) Ceftriaxone + azithromycin if STD related

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Cardiovascular			
Endocarditis			
Native valve	Staph. aureus Strep. viridian group Strep. gallolyticus Enterococcus HACEK group	1) Ceftriaxone + vancomycin + gentamicin	1) Ceftriaxone + daptomycin + gentamicin 2) Vancomycin + gentamicin 3) Ampicillin or ciprofloxacin If HACEK microorganism.
Prosthetic valves	Staph. aureus Staph. epidermis Strep. viridian group Enterococcus	1) Vancomycin + gentamicin + rifampin	1) Vancomycin + cefepime or imipenem + gentamicin
Fungal	Aspergillus Candida species	1) Voriconazole 1) Micafungin or caspofungin 2) Fluconazole + amphotericin B	1) Amphotericin B 1) Amphotericin B + flucytosine
Pericarditis			
Bacterial	Staph. aureus Strep. pneumoniae Neisseria meningitidis Enterobacteriaceae H. Influenzae (children)	1) Vancomycin + ceftriaxone	1) Vancomycin or daptomycin + ciprofloxacin
Fungal	Histoplasma capsulatum	1) Itraconazole + prednisone	1) Amphotericin B
TB	*M. tuberculosis*	1) Treatment is same as primary tuberculosis. See Section 4.6	
Lyme disease AV-block	Borrelia burgdorferi	1) Doxycycline 2) Amoxicillin	1) Ceftriaxone
Mycotic aneurysm	Staph. aureus Staph. epidermidis Salmonella species	1) Vancomycin + ceftriaxone	1) Piperacillin-tazobactam + vancomycin 2) Ciprofloxacin + vancomycin
IV line or catheter associated infection	Staphylococcus species *Enterococcus faecalis* Gram−ve bacteria	1) Vancomycin ± piperacillin-tazobactam (if gram -ve bacteria are suspected)	2) Daptomycin ± piperacillin-tazobactam
	Candida species	1) Micafungin	1) Caspofungin 2) amphotericin B
Bone			
Osteomyelitis			
Without vascular insufficiency	Staph. aureus Group a streptococcus Gram -ve bacilli	1) Vancomycin + ceftriaxone 2) Nafcillin or oxacillin + ceftriaxone	1) Vancomycin + cefepime

With vascular insufficiency	Staph. aureus Group a streptococcus Gram -ve bacilli Anaerobic bacteria	1) Revascularization 2) Vancomycin + meropenem or ertapenem 3) Vancomycin + moxifloxacin	1) Doxycycline 2) Clindamycin 3) Amoxicilin-clavulanate
Septic arthritis			
STD	N. Gonorrhea	1) Ceftriaxone + azithromycin	1) Doxycycline
Non-STD	Staph. aureus Streptococcus species Gram -ve bacilli	1) Vancomycin + ceftriaxone 2) Vancomycin + cefepime	1) Vancomycin + ciprofloxacin or levofloxacin
Prosthetic joints	Staph. epidermidis Staph. aureus Streptococcus species Enterococcus Gram -ve bacteria Pseudomonas species	1) Nafcillin or oxacillin + rifampin × 6 weeks followed by fluoroquinolone + rifampin × 3–6 months. 2) Cefepime + tobramycin if pseudomonas is suspected	1) Daptomycin + rifampin ± ciprofloxacin or ertapenem if gram -ve bacteria are suspected.
Diabetic foot infection	Staph. aureus Strep. agalactiae Strep. pyogenes Anaerobes	Superficial infection 1) Cephalexin 2) TMP-SMX Deep infection 1) Amoxicillin-clavulanate + TMP-SMX 2) Ampicillin-sulbactam + vancomycin	1) Doxycycline 2) Ciprofloxacin or levofloxacin 1) Ertapenem + vancomycin 2) Piperacillin-tazobactam + vancomycin
Neutropenic fever			
Bacterial	Pseudomonas species Enterobacteriaceae Staphylococcus species Streptococcus species	1) Cefepime ± tobramycin ± vancomycin 2) Meropenem ± tobramycin ± vancomycin	1) Ciprofloxacin or levofloxacin ± vancomycin or daptomycin

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Fungal	Candida species Aspergillus	1) Voriconazole for candida prophylaxis 2) Caspofungin or micafungin	1) Amphotericin B
Viral	Respiratory virus HSV, VZV	1) Acyclovir	
Sexually transmitted diseases			
Bacterial			
Syphilis	*T. pallidum*	Primary, secondary, and early latent syphilis. 1) Benzathine penicillin G Late latent syphilis 1) Penicillin G Neurosyphilis 1) Penicillin G	 1) Doxycycline 2) Ceftriaxone 1) Penicillin G 1) Ceftriaxone 2) Desensitize the patient if penicillin allergy
Gonorrhea	N. Gonorrhea	1) Ceftriaxone	1) Azithromycin + gentamicin
Chlamydia	*Chlamydia trachomatis*	1) Azithromycin 2) Doxycycline	1) Erythromycin 2) Amoxicillin
Chancroid	H. ducreyi	1) Ceftriaxone 2) Azithromycin	1) Ciprofloxacin 2) Erythromycin
Lymphogranuloma venereum	*C. trachomatis*	1) Doxycycline 2) Erythromycin	1) Azithromycin
Granuloma inguinale	Klebsiella granulomatis	1) TMP-SMX 2) Azithromycin	1) Doxycycline 2) Ciprofloxacin
Viral			
Warts	Human papillomavirus	1) Podofilox lotion 2) Imiquimod 5% cream	1) Sinecatechins
Genital herpes	HSV types 1 and 2	1) Acyclovir 2) Valacyclovir	1) Famciclovir
Molluscum contagiosum	Molluscum contagiosum virus (poxvirus)	1) Lesions regress themselves in 1–2 years. 2) Curettage, cryosurgery, laser therapy	1) Cantharidin 2) Tazarotene
HIV infection	HIV	See Section 6.13	See Section 6.13
Parasitic			
Trichomoniasis	T. vaginalis	1) Metronidazole PO	1) Tinidazole PO
Scabies	Sarcoptes scabiei	1) Permethrin 5% topical	1) Ivermectin PO
Pediculosis pubis	Pubic louse	1) Permethrin 1% topical 2) Malathion 0.5% topical	1) Ivermectin PO

Note: See Section 9.17, for more information for the choice of antibiotics.

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10

Drugs, dosages, side effects, and pregnancy catagory

Drug	Adult dosage	Children dosage	Dose adjustment In kidney/Liver problem	Side effects	Pregnancy category
Beta-lactam					
Pen VK (PO)	250–500 mg q6-8h	25–75 mg/kg/day Divided into q6-8h	No	Allergic reaction, N/V, and diarrhea	B
Pen G (IV, IM)	0.5–4 MU q4-6h	0.5–3 MU q4-6h	CrCl <50 → q8h dosing CrCl <10 → q12h	Same as above	B
Aminopenicillin					
Amoxicillin	500–1000 mg q8h (PO)	25–100 mg/kg/day Divided into q8–12h	CrCl 10–30 → 1 gm q12h CrCL <10 → 1 gm q24h	Allergic reaction, N/V, diarrhea, crystalluria, and renal insufficiency due to tubular obstruction	B
Amoxicillin-clavulanate	500/125 mg q8h 875/125 mg q12h	Dosing based on Amox 45–90 mg/kg/day (div q12h)	CrCl <30 → q12h CrCl <10 → q24h	Allergic reaction, N/V, diarrhea, rash, *Clostridium difficile* colitis, and hepatotoxicity	B
Ampicillin	250–500 mg q6h (oral) 1–2 gm q4-6h (IV)	200–400 mg/kg/day (divide q6h) IV	CrCl <30 → q8-12h CrCl <10 → q12	Same as above	B
Ampi-sulbactam	3–9 gm q8h (sum of ampi + sulb)	100–300 mg/kg/day (div into q6h)	CrCl <30 → q12h CrCl <15 → q24h	Same as above + eosinophilia	B
Antipseudomonal penicillin/antistaphylococcus					
Piperacillin (IV)	2–4 gm q4–6h	100–450 mg/kg/day (divided q6h)	CrCl 10–50 → 3–4 gm q6-8h CrCl <10 → 3–4 gm q8h	Same as above + platelet dysfunction	B
Piperacillin-tazobactam	3.375–4.5 gm	300 mg/kg/day Q6–8h (divide q6h)	CrCl 20–40 → 2.25 –3.375 gm q6h CrCl <20 → 2.25 gm q6-8h	Same as above + thrombocytopenia, and acute kidney injury	B

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Drug	Adult dosage	Children dosage	Dose adjustment In kidney/Liver problem	Side effects	Pregnancy category
Anti-Staph Pen Dicloxacillin (oral)	125—500 mg Divided into q6h	12.5—100 mg/kg/day	No adjustment	Fever, rash, N/V, diarrhea, *C. difficile* colitis, and eosinophilia	B
Nafcillin (IV/IM)	2 gm q4h	150—200 mg/kg/day	No adjustment	Same as all beta-lactams + neutropenia	B
Oxacillin (IV)	2 gm q4h	150—200 mg/kg/day Divided into q6h	No adjustment	Same as above; neutropenia is rare in children, rash, and liver toxicity is more common than nafcillin	B
Cephalosporin (First generation)					
Cefadroxil (PO)	500—1000 mg q12h	30 mg/kg/day	CrCl 10—50 → 500 mg q12h CrCl <10 → 500 mg q36h	Rash, neutropenia, serum sickness, *C. difficile* colitis, diarrhea, ↑liver enzymes, thrombocytopenia, and positive comb test hypersensitivity	B
Cephalexin (PO)	250—1000 mg q6h Max 4 gm/day	25—100 mg/kg/day (div q6h)	CrCl 10—50 → 500 mg q8-12h CrCl <10 → 500 mg q24—48h	Same as above	B
Cefazolin (IV/IM)	1—2 gm q8h 3 gm if > 120 kg	50—150 mg/kg/day (divide q6h)	CrCl 10—50 → 1—2 gm q12h CrCl <10 → 1—2 gm q24h	Same as above	B
Second generation					
Cefuroxime (PO)	250—500 mg q12h	20—30 mg/kg/day	CrCl 10—30 → q12h CrCl <10 → q48h	Same as above	B
Cefuroxime (IV/IM)	750—1500 mg q8h	150 mg/kg/day (divide q8h)	CrCl 10—50 → 0.75—1.5 gm q12h CrCl <10 → 0.75—1.5 gm q48h	Same as above	B
Loracarbef (PO)	200—400 mg qd-bid	15—30 mg/kg/day	No adjustment	Same as above	B
Cefaclor (PO)	250—500 mg q8—12h	20—40 mg/kg/day	CrCl <10 → q12h	Same as above	B
Cefprozil (PO)	250—500 mg po Q12h	15—30 mg/kg/Day (div q12h)	CrCl 10—50 → 500 mg q24h CrCl <10 → 250 mg q12h	Same as class cephalosporin	B
Cefoxitin (IV)	2 gm q6-8h	80—160 mg/kg/day (div q6-8h)	CrCl 10—50 → q8—12h CrCl <10 q24-48h	Same as above	B

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Drug	Adult dosage	Children dosage	Dose adjustment In kidney/Liver problem	Side effects	Pregnancy category
Cefotetan (IV/IM)	1—3 gm q12h	60—100 mg/kg/day (div q12h)	CrCl 10—30 → 1-2 gm q24h CrCL <10 → 1—2 gm q48h	Same as above + hemolytic anemia ↑PT/PTT, and bleeding ulcers	B
Third generation					
Cefotaxime (IV)	1—2 gm q6-8h	100—200 mg/kg/day (div q6-8h)	CrCl 10—50 → 2 gm q12-24h CrCl <10 → 2 gm q24h	Phlebitis, rash, N/V, diarrhea, *C. difficile* colitis, positive comb test, and allergic reaction. These side effects are share with all cephalosporin	B
Ceftriaxone (IV/IM)	1—2 gm q12-24h	50—100 mg/kg/day (div q12-24h)	No	Same as above + pseudo-cholelithiasis, and drug-induced thrombocytopenia	B
Ceftizoxime (IV)	1—2 gm q8-12h	150—200 mg/kg/day	CrCl 10—50 → 2 gm q8-12h CrCl <10 → 2 gm q24h	Same as all other cephalosporin	B
Ceftazidime (IV/IM)	1—2 gm q8-12h	150—200 mg/kg/day (div q8h)	CrCL 10—50 → 1—2 gm q12-24h	Same as all other cephalosporin + CNS effects such as seizure and coma	B
Ceftazidime-avibactam (IV)	2.5 gm q8h	50—62.5 mg/kg q8h	CrCL 31—50 → 1.25 gm q8h CrCL 16—30 → 0.94 gm q12h CrCl <16 → 0.94 gm q24h	Same as above	B
Cefdinir (PO)	300 mg q12h	14 mg/kg/day (div q12h)	CrCL <30 → 300 mg q24h	Same as all other cephalosporin. Red stool if taken with iron	B
Cefixime (PO)	800 mg × 1 (Gonococcal) 400 mg qd x 10 days (Strep pharyngitis)	8 mg/kg/day (divide into q12 or 24h)	CrCl 10—50 → 300 mg qd CrCl <10 → 200 mg q24h	Same as all other cephalosporin	B
Cefpodoxime (PO)	200 mg × 1 (Gon) 200 mg q12h	10 mg/kg/day (div q12h) Max 400 mg/day	CrCl 10—50 → 200 mg bid CrCl <10 → 200 mg qd	Same as all other cephalosporin + rare cases of acute liver injury, and pulmonary infiltrates	B
Fourth generation					
Cefepime (IV)	1—2 gm q8—12h	100—150 mg/kg/day (divide q8-12h)	CrCl 30—60 → 2 gm q12h CrCl 29—11 → 1 gm q24h	Same as all other cephalosporins + neurotoxicity such as confusion, disorientation, agitation, abnormal behavior, and hallucination. FDA warning	B

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Drug	Adult dosage	Children dosage	Dose adjustment In kidney/Liver problem	Side effects	Pregnancy category
			CrCl <11 → 500 mg q24h	→ may cause nonconvulsive status epilepticus in renal insufficiency patients if dose is not adjusted. (inhibit competitively GABA)	
Fifth generation					
Ceftaroline (IV)	600 mg q12h	6–8 mg/kg q8h	CrCl 30–50 → 400 mg q12h CrCl 29–15 → 300 mg q12h CrCl <15 → 200 mg q12h	Same as all other cephalosporins + eosinophilic pneumonia, and reversible neutropenia	B
Carbapenem					
Imipenem-Cilastin (IV)	500–1000 mg q6-8h	15–25 mg/kg q6h	CrCL 30–60 → 300 mg q6h CrCL 15–30 → 200 mg q6h CrCl <15 → 200 mg q6h	General common to all carbapenem → phlebitis sickness, positive comb test, fever, rash, neutropenia, eosinophilia, thrombocytopenia N/V, diarrhea, *C. difficile* colitis, headache, confusion, and ototoxicity Specific: Seizure x 10 ↑risk, renal toxicity	C
Meropenem (IV)	1 gm q8h. Meningitis 2 gm q8h	60–120 mg/kg/day Divide into q8h	CrCL 25–50 → 1 gm q12h CrCl 10–25 → 500 mg q12h CrCl <10 → 500 mg q24h	Same as above but low risk of seizure	B
Ertapenem (IV/IM)	1 gm q24h	30 mg/kg/day Divide q12h	CrCl <30 → 500 mg q24h	Same as above + muscles weakness, and visual hallucinations	B
Doripenem	500 mg q8h	Not recommended	CrCL 30–50 → 250 mg q8h CrCl 10–30 → 250 mg q12h CrCl <10 →do not use it	Same as all other carbapenem ↑mortality rate and poorer cure rate for the treatment of VAP, not recommended for pneumonia	B
Monobactam					
Aztreonam (IV)	0.5–2 gm q6-8–12h	90–120 mg/kg/day	CrCl 10–50 →1–1.5 gm q8h CrCl <10 →1–2 gm q24h	Same as all other carbapenem No cross-sensitivity with penicillin	B
Lipoglycopeptide					
Vancomycin (IV)	Based on AUC_{24} 400–600 ug/ml	Same AUC_{24}	↓the dose according to AUC_{24}	Red man syndrome due to rapid infusion ↑slow the infusion and give antihistamine and	C

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Drug	Adult dosage	Children dosage	Dose adjustment In kidney/Liver problem	Side effects	Pregnancy category
				acetaminophen one to two hour before infusion, eosinophilia (HLA-A*32:01 ↑risk), and drug-induced immune thrombocytopenia	
Continue-Vancomycin (IV)				Drug-induced neutropenia, nonreversible ototoxicity, reversible nephrotoxicity, and IgA bullous dermatitis	C
Vancomycin (oral)	125—500 mg q6h	40 mg/kg/day (divide q6h)	None	Not absorbed into the system	C
Dalbavancin	1 gm × 1 then 500 mg in once weekly or 1500 mg × 1 than 1000 mg q 2 weeks.	18—22.5 mg/kg × 1	CrCL <30 → 750 mg × 1 then 375 mg in 1 week	N/V, diarrhea, headache, rash, red man syndrome myopathy, rhabdomyolysis, and ↑liver enzymes	No data
Linezolid (PO/IV)	400—600 mg q12h	10 mg/kg q8h	None	Rash, N/V, diarrhea, ↑liver enzymes, *C. difficile* colitis, longer therapy >2 weeks: reversible myelosuppression, thrombocytopenia, neutropenia ↑risk of kidney injury, lactic acidosis, and peripheral and optic neuropathy	C
Daptomycin	4—12 mg/kg q24h	5—10 mg/kg q24h	CrCl <30 → 6 mg q48h	Myopathy, eosinophilic pneumonia, phlebitis, rash, N/V, diarrhea, headache, and ↑risk of *C. difficile* colitis	B
50s ribosomal subunit inhibitors					
Macrolide				General side effects apply to all macrolides include: GI: anorexia, N/V, diarrhea, and stomach ache QTc prolongation, tinnitus, and liver inflammation	
Azithromycin (IV, PO)	500 mg IV daily 500 mg po × 1 250 mg × 2—5 days	10 mg/kg/day (IV) 5—12 mg/kg/day (oral)	None	Same as above but with less frequency	B
Clarithromycin (PO)	250—500 mg bid	15 mg/kg/day (q12h)	CrCL <10 → 500 mg q24h	Same as other macrolide	C

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Drug	Adult dosage	Children dosage	Dose adjustment In kidney/Liver problem	Side effects	Pregnancy category
Erythromycin (PO, IV)	250—500 q6-12h	40—50 mg/kg/day (q6h)	None	Same as other macrolide, but GI symptoms are more severe	B
Clindamycin (PO, IV)	150—450 mg q6-8h (PO) 300—900 mg q8h (IV)	30—40 mg/kg/day PO (q6-8h) 20—40 mg/kg/day IV (q6-8h)	None	Rash, fever, allergic reaction, ↑liver enzymes, *C. difficile* colitis, diarrhea, N/V, neutropenia, thrombocytopenia, and eosinophilia	B
Chloramphenicol (IV)	50—100 mg kg/day (q6h) Max 4 gm/day	50—100 mg/kg/day (q6h) max 4 gm/day	None	Fever, rash, diarrhea, headache, neutropenia, thrombocytopenia, aplastic anemia, and gray baby syndrome	C
30s ribosomal subunit inhibitors					
Tetracycline (PO)	250—500 mg q6h	Not recommended 25—50 mg/kg/day (q6h) For >8 years old	CrCl 10—50 →q12-24h CrCl <10 q24h	Rash, N/V, diarrhea, discoloration of teeth, photosensitivity, and pseudotumor cerebri	D
Minocycline (PO/IV)	100 mg q12h	Do not use for age <8 years 4 mg/kg/day (q12h)	None	Same as above + vertigo, and ataxia	D
Doxycycline (PO, IV)	100 mg q12h	Can be use in children for <21 days (AAP) 2—4 mg/kg/day (q12h)	None	Same as other tetracyclines. Possibility of discoloration of teeth is less than other TCN	D
Amino-glycoside				Renal tubular necrosis, deafness, vertigo, and rash N/V and diarrhea are general side effects Associated with all aminoglycosides	D
Amikacin	7.5 mg/kg q 12h peak 15—30 ug/ml Trough 5—10 ug/ml Or 15 mg/kg/day Peak 56—64 ug/ml Trough <1 ug/ml	15—20 mg/kg/day	CrCL 10—50 → 7.5 mg/kg q24h CrCl <10 → 7.5 mg/kg q48h	Same as all other aminoglycoside	D
Gentamycin	1.7—2 mg/kg q8h T.P 4—10 ug/ml T.T 1—2 ug/ml 5—7 mg/kg/day T.T < 1 ug/ml	2.5 mg/kg q8h or 5—7 mg/kg/day	CrCl 10—50 → 1.7 —2 mg/kg q12-24h CrCl, 10 → 1.7 mg/kg q48h	Same as all other aminoglycoside	D

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Drug	Adult dosage	Children dosage	Dose adjustment In kidney/Liver problem	Side effects	Pregnancy category
Tobramycin	2 mg/kg q8h T.P 4—10 ug/ml Or 5—7 mg/kg/day T.T < 1 ug/ml	2.5 mg q8h Or 5—7 mg/kg/day	CrCl 10—50 →2 mg/kgq12-24h CrCl <10 → 2 mg/kg q48h	Same as all other aminoglycosides	D
Streptomycin (IM/IV)	15 mg/kg IM q24h (tuberculosis) 15 mg/kg IM q12h (plague and tularemia)	20—40 mg/kg IM q24h (tuberculosis) 15 mg/kg q12h (other infections)	CrCL 10—50 → 15 mg/kg q24-72h CrCl <10 15 mg/kg q72-96h	Same as all other aminoglycosides	D
Neomycin (topical, PO)	1 gm PO @ 1, 2 and 11 p.m. on the day of surgery	Not recommended	None	Not given IV or IM	D
DNA gyrase and topoisomerase inhibitors					
Fluoroquinolones		Not recommended In children <16 years old Except in the tx of anthrax, complicated UTI and pyelonephritis	Yes	General: CNS: Confusion, light headedness, psychosis, pseudotumor cerebri, muscles weakness in pt with myasthenia gravis, aortic aneurysm ↑FDA issue safety warning, tendinopathy ↑ages >60 years (achilles tendon rupture (2%—6%)), QTc prolongation, GI distress, *C. difficile* colitis, thrombocytopenia, hypoglycemia, and photosensitivity	C
Ciprofloxacin (PO, IV, top)	250—750 mg q12h 500—1000 mg XR q24h 200—400 mg q8-12h (IV)	20—40 mgkg/day PO (q12h) 20—30 mg/kg/day IV (q12h0)	CrCl 30—50 → ↓the dose and give q12h CrCl <30 → dose q18-24h	Same as above, higher risk of QTc prolongation as compared to levofloxacin	C
Delafloxacin (IV, PO)	300—450 mg q12h (IV) 450 mg PO q12h	Not approved	Based on eGFR	Same as all other FQ except not associated with QTc prolongation and photosensitivity	No Data
Gatifloxacin Not available in the United States	200—400 mg q24h (PO, IV)	Not approved	CrCl <50 → 400 mg x 1 than 200 mg q24h	Same as all other FQ. Associated with higher incidence of dysglycemia removed from US market	C
Gemifloxacin Not available in the United States	320 mg po q24h	Not approved	CrCL <50 → 160 mg q24h	Same as all other FQ Duration depended on skin rash (>14 days)	C

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Drug	Adult dosage	Children dosage	Dose adjustment In kidney/Liver problem	Side effects	Pregnancy category
Levofloxacin (IV, PO, top)	250—750 mg q24h (IV, PO)	16—20 mg/kg/day (div q12h)	CrCl 20—50 → 750 mg q48h CrCl <20 → 750 mg x 1 then 500 mg q48h	Same as any other FQ	C
Moxifloxacin (PO, IV)	400 mg q24h	Not approved	None	Same as any other FQ	C
Norfloxacin (PO)	400 mg bid	Not recommended	CrCl <30 → 400 mg q24h	Same as other FQ	C
Ofloxacin PO, Opth	200—400 mg q12h (PO)	Not recommended	CrCl 10—50 → 200—400 mg q24h CrCl <10 → 200 mg q24h	Same as other FQ	C
Folic acid metabolism inhibitors					
TMP/SMZ (PO, IV)	160—800 mg bid (PO) 5—20 mg/kg/da (IV) Divide q6-12h	5—20 mg/kg/day (IV) divide into q12h	CrCl <30 5—10 mg/kg/day divide into q 12h	Headache, confusion, photosensitivity kernicterus in neonates, steven Johnson syndrome, N/V, diarrhea, pancreatitis, agranulocytosis, aplastic anemia, hemolysis in G6PD deficiency, methemoglobinemia, thrombocytopenia, crystalluria, interstitial kidney injuries, and acute tubular necrosis	C
Miscellaneous					
Metronidazole (PO, IV)	250—500 mg TID (PO) 7.5 mg/kg q6-8h (IV)	30—40 mg/kg/day (PO) divide q6h 22.5—40 mg/kg/day (IV) Divide q6-8h	CrCL <10 → 7.5 mg/kg q12h	Metallic taste, peripheral or optic neuropathy, aseptic meningitis/encephalitis, and disulfiram like reaction with alcohol	B
Quinupristin —Dalfopristin (IV)	7.5 mg/kg q12h	Not recommended	None	Phlebitis require central line, myalgia, arthralgia, nausea, and ↑unconjugated bilirubin	B
Tigecycline (IV) FDA warning ↑mortality	100 mg × 1 then 50 mg q12h	Not recommended	None	N/V, photosensitivity, pseudotumor cerebri, pancreatitis, phlebitis, rash, ↑LFT, and ↑BUN	X
Non-HIV antiviral drugs					
Acyclovir	400—800 mg q8h to 5 times a day (PO) 5—12.5 mg/kg q8h (IV)	30—60 mg/kg/day divided q8h	CrCL 10—50 →5—12.5 mg/kg q12-24h CrCl <10 → 2.5—6.25 mg/kg Q24h	N/V, diarrhea, hallucination, involuntary movement vertigo, tremor, confusion, may crystallize in renal tubules and cause obstruction, ↑creatinine, and hematuria	B

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Drug	Adult dosage	Children dosage	Dose adjustment In kidney/Liver problem	Side effects	Pregnancy category
Famciclovir	250—1000 mg bid-tid (PO)	None	CrCl 10—50 → 500 mg q12-24h CrCl <10 → 250 mg q24h	Same as above	B
Valacyclovir (prodrug)	500—1000 mg bid to tid (PO)	60 mg/kg/day Divide into q8h (PO)	CrCl 10—50 → 1000 mg q12-24h CrCl <10 → 500 mg q24h	Same as above	B
Ganciclovir	5 mg/kg q12-24h (IV)	5—12 mg/kg/day (IV) divide into 12—24h	CrCL 10—50 → 1.25—2.5 mg/kg q24h CrCl <10 → 1.25 mg/kg 3 x/week	Neutropenia, thrombocytopenia, N/V, diarrhea abdominal pain, rash, confusion, headache, seizure, and retinal detachment	C
Valganciclovir (prodrug)	900 mg q12h (PO)	32 mg/kg/day (PO) divide into q12h	CrCl <60 → 450 mg q12h CrCL <40 → 450 mg q24h CrCl <25 → 450 mg q48h CrCL <10 →do not use	Black box warning → neutropenia, thrombocytopenia anemia, fertility impairment, mutagenic and carcinogenic, and teratogenic	X
Cidofovir	5 mg/kg IV once a Wk X 2wk, then qowk	3—5 mg/kg IV once a wk	CrCl <50 →Do not use	Black box warning → nephrotoxicity with or after two doses. N/V, fever, alopecia, iritis or uveitis, neutropenia, myalgia, carcinogenic and teratogenic, ↓sperm counts, and fertility	C
Foscarnet	60—90 mg q8-12h (induction) 90—120 mg q24h (maintenance)	120—180 mg/kg/day (divided into q8-12h)	Dose adjustment based on CrCL divided by weight in Kg	Nephrotoxicity, anemia, ↑liver enzymes, headache, nausea, seizure, fever, neuropathy, and penile and oral ulcers	C
Amantadine and rimantadine	100 mg po bid <65 yrs 100 mg qd > 65 yrs	None	CrCl 10n-(-)50 → 100 mg q24h CrCL <10 → 100 mg q7 days	Nervousness, confusion, lightheadedness, hallucination, delirium, seizure, psychiatric issue, and nausea	C
Oseltamivir	75 mg po bid	30—75 mg bid Depending upon weight	CrCl 30—60 → 30 mg bid CrCl 10—30 → 30 mg qd	N/V, diarrhea, headache, rash, delirium, and abnormal behavior	Not Rated
Zanamivir (oral inh)	Inhale 10 mg po bid	>7 yrs 10 bid Inhalation	None	Cough, sinusitis, N/V, diarrhea, and psychiatric issue	C
Veramivir	600 mg IV x 1	None	CrCl 31—50 → 200 mg q24h CrCl 10—30 → 100 mg q24h CrCl <10 → 100 mg × 1 then 15 mg q24h	N/V, diarrhea, insomnia, and hypertension	C

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Drug	Adult dosage	Children dosage	Dose adjustment In kidney/Liver problem	Side effects	Pregnancy category
Ribavirin	Various; see manufacturing guideline	See manufacturing guideline	None	Hemolytic anemia, retinal detachment, hearing impairment, and hypersensitivity reaction	X
Interferon Alfa 2a, 2b	Varies based on diagnosis. Check manufacturing guide	None	None	Black box warning → neuropsychiatric problems, flue-like syndrome at the beginning of the therapy, depression, anxiety, reversible hearing loss, and optic neuropathy	C
Antifungal					
Amphotericin B Lipid complex/ liposomal	3—5 mg/kg daily	3—5 mg/kg/day	None	Nephrotoxicity, fever, chills, N/V, rash, electrolyte abnormality, phlebitis, and anemia	B
Azoles-Fluconazole (IV, Po)	100—400 mg q24h	6—12 mg q24h	CrCl <50 ↓dose 50%	N/V, headache, rash, abdominal pain, diarrhea, ↑liver enzymes, hepatotoxicity (rare), and alopecia	C/D
Itraconazole (PO, IV)	200—600 mg q24h	5—10 mg/kg/ day	CrCL 10—50 → 100 —200 mg PO q12h. Do not use IV if CrCL< 30 CrCL <10 → 50—100 mg po Q12h	N/V, abdominal pain, diarrhea, hepatitis and acute liver, failure, delirium and peripheral neuropathy, hypertension, and hypokalemia	C
Voriconazole	IV = 6 mg/kg × 2 doses Then 3—4 mg/kg q12h PO= > 40 kg 400mgq12 X 2 then 200 mg q12h <40 kg → 200 mg q12h X2, then 100 mg q12h	IV = 2—12yrs→ 6 mg/kg × 2 then 4—8 mg q12h PO = 9 mg/kg q12h	CrCl <50 →do not use IV ↓the dose in liver dysfunction	N/V, abdominal pain, diarrhea, hepatitis, photosensitivity, ↑risk of skin cancer, neurotoxicity, and visual disturbance	D
Echinocandins-Micafungin (IV)	100—150 mg q24h	1—3 mg/kg/day (max 150 mg)	None	N/V, headache, ↑liver enzymes, hepatitis (rare), and ↓kidney function (rare)	C
Caspofungin	70 mg × 1 then 50 mg q24h 150 mg qd for endocarditis	70 mg/m2 × 1 then 50mg/m2 q24h max 70 mg/day	↓dose in hepatic insufficiency	Pruritis at infusion site, headache, n/v, diarrhea, and reversible thrombocytopenia	C

Further reading

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'*Note:* Page numbers followed by "f" indicate figures, "t" indicate tables and "b" indicate boxes.'

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DEVELOPMENTS IN MICROBIOLOGY

INFECTIOUS DISEASES: SMART STUDY GUIDE FOR MEDICAL STUDENTS, RESIDENTS, AND CLINICAL PROVIDERS

SAIF UL ISLAM, MD., RPH., BCPS
Adventist Hospital, California, USA

Infectious Diseases: Smart study guide for medical students, residents, physicians, clinical pharmacists, nurses, and physician assistants attempts to consolidate knowledge and information into a step-by-step process that would be easy to understand, remember, and apply in a clinical setting. High-yield information presented in this book is necessary for medical students and residents. This book has provided information for all disciplines working in infectious diseases, whether students, residents, physicians, pharmacists, or nurses. The book is organized for quick and easy to retrieve information for all professionals.

Key Features

- Medical and pharmacotherapeutic information about infectious diseases are combined into one bookConsolidates knowledge and information on infectious diseases
- Presents content that is easy to understand, remember, and apply in a clinical setting
- High-yield information for students and residents

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